Towards hybrid stochastic modeling and simulation of complex systems in multi-scale environments

With case studies on the spread of tuberculosis in Democratic Republic of the Congo

by

Selain Kasereka Kabunga

submitted in accordance with the requirements for
the degree of Doctor of Philosophy

in the subject

Applied Mathematics

College of Science, Engineering & Technology (CSET)
Department of Mathematical Sciences

at the

University of South Africa

Supervisor: Prof. Dr. Emile Franc Doungmo Goufo
Joint co-supervisor: Prof. Dr. Vinh Ho Tuong (Vietnam National Univ.)

October 2020

Preface

This thesis is the achievement of my academic career as a PhD student. It was written to fulfill the requirements for the degree of Doctor of Philosophy in Applied Mathematics in the Department of Mathematical Sciences in the College of Science, Engineering and Technology (CSET) at the University of South Africa. It was supervised by Professor Dr. Emile Franc Doungmo Goufo from the same University and co-supervised by Professor Dr. Vinh Ho Tuong from the Vietnam National University in Hanoi. It is an original work of the author and has not been submitted in any form to any degree or diploma in any other institution. Where use has been made of works by other authors, they have been duly acknowledged.

The thesis entitled «*Towards hybrid stochastic modeling and simulation of complex systems in multi-scale environments: with case studies on the spread of tuberculosis in the Democratic Republic of the Congo* », is presented in accordance with several research carried out during 3 years. It focused on modeling and simulation of complex systems, more specifically the spread of tuberculosis in the population with case studies from DRC using real data. I essentially exploited the notions of differential equations from applied mathematics and the notions of multi-agent systems from artificial intelligence and robotics. The situation of tuberculosis in DRC, which remains endemic, motivated me personally to work on the topic in order to contribute to the control of this disease in my country as a researcher.

This Thesis will especially appeal to epidemiologists, clinicians, public health specialists, bio-statisticians, bio-mathematicians, data scientists and artificial intelligence engineers with a taste for mathematics and statistics, but also to those who enjoy modeling and simulating complex systems, including the spread of tuberculosis in different environments.

The process of researching and writing this thesis began in 2017. It is true that the research undertaken was complex, but it allowed me to answer the questions raised in the topic in detail with the complicity of my supervisors who were always available.

I hope you will enjoy your reading !

Selain Kasereka Kabunga

Summary

Mathematical modeling of the spread of infectious diseases in a population has always been recognized as a powerful tool that can help decision-makers understand how a disease evolves over time. With the evolution of science and humanity, it has become evident that Mathematical models are too simplistic and have some limitations in modeling environmental phenomena, such as the spread of epidemics in a population, when they are applied without combining them with other sciences. In understanding the dynamics of epidemics in a population, the weakness of these models is their difficulty in grasping the complexity inherent in the spread of diseases in real life because, life is supported by human interactions and behaviors that are understood through networks of social and spatial interactions. Modeling the spread of epidemics which takes this reality into account requires the implementation of new tools to refine the results already obtained by mathematical models.

The aim of this thesis is to explore and attempt to extend new developments in mathematical modeling of the spread of infectious diseases by proposing new tools based on mathematical models from differential equations and agent-based models from intelligent agents derived from artificial intelligence. To achieve this objective, the study starts from a comparative study of two ways of modeling and simulation of the spread of infectious diseases in the population, namely mathematical modeling and agent-based modeling with a concrete case study of the spread of tuberculosis based on data from the Democratic Republic of the Congo (DRC). Then comes a coupling study of these two approaches in a single model and its implementation in a multi-scale environment.

The results show that the coupled model is more realistic compared to mathematical models generally implemented in the literature. Four case studies are presented in this thesis. Mathematical modeling based on differential equations is used in the first and second cases. The third case is based on intelligent agents model while the last one is based on the coupling of mathematical models and agent-based models. Application of implemented models to the spread of tuberculosis reveals that detection of people with latent tuberculosis and their treatment are among the actions to be taken into account in addition to those currently carried out by the Congolese health system. The models assert that the current TB situation in DRC remains endemic and that the necessary measures need to be taken to reduce the burden of TB, especially to control it, through the tuberculosis elimination strategy and its elimination in the future in accordance with the Sustainable Development Goals. Our hybrid model benefiting from the advantages of EBM and ABM confirms that taking the individual into account as a fully-fledged entity and managing their behavior gives the microscopic aspect of the model set up and brings it closer as much as possible to reality. Mathematical management of the spread of the disease in cities gives a macroscopic aspect

to the model. Numerical simulations of this last model on a multi-scale virtual environment affirm that the mobility of individuals from city to city has a significant impact on the spread of tuberculosis in the population. Controlling the rate of population mobility from one city to another is one of the most important measures for large-scale disease control. This model therefore draws its richness from this dynamic at two different scales (two time scales modeling approaches: at the microscopic/individual level (ABM) and macroscopic/city level (ODE)), which gives the emergence of the model at the global level. As a result, it seems that the coupling of mathematical models to agent-based models should be applied when the dynamics of the complex system under consideration is at different scales.

Based on our research results, it seems that the choice of an approach must depend on how the modeler would like to achieve the expected results. Mathematical models remain essential due to their analytical and synthetic aspect, but their coupling with intelligent agent-based models makes it possible to refine known results and thus reflect the reality of real life, because the resulting model integrate interactions of individuals and their heterogeneous behaviors that are necessary for understanding the spread of infectious diseases in the population that only mathematical models based on differential equations can not capture.

Key terms: Mathematical modeling; Differential equations; Agent-based modeling; simulation; Hybrid model; Stochastic; Tuberculosis; Democratic Republic of the Congo; Mobility; Multi-scale environment; Complex systems; Mixed population structure; A 4-level population structure; Virtual environment; Microscopic; Macroscopic; Multi-agent systems, GAMA Platform.

Declaration 1 - Plagiarism

Name: Kasereka Kabunga Selain
Student number: 64021165
Degree: Doctor of Philosophy

Towards hybrid stochastic modeling and simulation of complex systems in multi-scale environments
With case studies on the spread of tuberculosis in the Democratic Republic of the Congo

I declare that the above thesis is my own work and that all the sources that I have used or quoted have been indicated and acknowledged by means of complete references.

I further declare that I submitted the thesis to originality checking software and that it falls within the accepted requirements for originality.

I further declare that I have not previously submitted this work, or part of it, for examination at Unisa for another qualification or at any other higher education institution.

Date: October 10, 2020.

Signature

Declaration 2 - Publications

Conference papers:

- A stochastic agent-based model and simulation for controlling the spread of tuberculosis in a mixed population structure,World Scientific Proceedings Series: Developments of Artificial Intelligence Technologies in Computation and Robotics, pp. 659-666 (2020). https://doi.org/10.1142/9789811223334_0079
- Agent-Based Modeling and Simulation for evacuation of people from a building in case of fire, The 9th Int. Conf. on Ambient Systems, Networks and Technologies (ANT2018), Procedia Computer Science 130, 10-17, (2018). https://doi.org/10.1016/j.procs.2018.04.006

Published and submitted papers

- Analysis and Simulation of a Mathematical Model of Tuberculosis Transmission in Democratic Republic of the Congo, in press (accepted for publication AIDE-D-20-01182), Advances in Difference Equations (2020).
- A Hybrid Model and simulation of Tuberculosis Outbreak in a population with a high mobility, submitted in Results in Physics, Manuscript Number: RINP-D-20-01391 (2020).
- Modeling and simulation of the evolution and control of drug-sensitive and multidrug- resistant tuberculosis in a resource-limited country, submitted in Biomedical Journal (2020).

Papers in preparation

- Agent-based model and simulation of tuberculosis dynamics with a 4-level pupulation structure in DRC.
- An single agent-based model to simulate Drug-Sensitive and Multidrug-Resistant Tuberculosis outbreak in RDC.

Date: October 10, 2020.

Signature

Dedication

To my wife Grace Kavira Basuwa;

To our sons Junias Kasereka Bayoli and St. Jaden Bayoli Lusi.

Acknowledgements

I would like to thank God for his love and thanks to whom I am still alive. The accomplishment of this work clearly testifies his love and mercy.

I express my sincere gratitude to **Professor Emile Franc Doungmo Goufo** for supervising this doctoral thesis, and for trusting me from our first exchanges up to this stage, he has been confident. His openness, curiosity and listening skills were of paramount importance. Indeed, it took just a while for the professor to see a better future for my research that should couple the notions of artificial intelligence (multi-agent systems) and the mathematical sciences, a field that he knows very well. This thesis is the result of his open-mindedness! Dear Professor, find here my sincere acknowledgments.

I would particularly like to thank **Professor Ho Tuong Vinh** for agreeing to join this work from Vietnam as co-supervisor. Apart from teaching me at the Vietnam National University of Hanoi, he directed my bibliographic research and expressed this desire to train me as a researcher.

I am indebted to the teaching staff of the Department of Mathematics and Computer Science of the Faculty of Sciences of the University of Kinshasa where I have been working for more than 10 years. To mention, Professors Alain Musesa, Ramadhani Issa, Rebecca Walo, Justin Dupar Kampempe, Saint Jean Djungu, Oscar Lungiambudila, Joseph Désiré Bukweli, Guillaume Muhindo, Pierre Kasengedia, Pascal Mubenga, Eugèene Mbuyi and particularly Professor Dr. Nathanaël Kasoro Mulenda, who is a scientific father to me. His hardworking way has proved to me that only work can raise academically a person.

I would like to acknowledge Professors Apollinaire Ndondo and Serge Bisuta who have been very useful to me in the concrete realization of this work. Their contributions were useful for the mathematical considerations of the implemented models and the creation of a bridge between the results obtained and tuberculosis disease.

I thank all my friends who recognize themselves for having supported me during all the time of dissertation research. I am thinking in particular of Emmanuel Mokoli, Thierry Fwamba, Dr. David MukebaKeb, Beni Lusanga, Firmin Fundji, Rodriguez Diwa, Papy Baruani and Petit Joachim Ndju.

I would like to thank the UNISA International Conference on Mathematical Sciences and Applications 2019 organizers, especially Professor Dr. Justin Munganga for inviting me to present the progress of my doctoral research. I also thank the International Francophone Institute (IFI) authorities of the Vietnam National University in Hanoi for accepting me as an intern for 4 months during my doctoral research. I had fruitful discussions with Benoit Gaudou and Kevin Chapuis during my visits to the ICT laboratory of the University of Science and Technology of Hanoi (USTH). May my thanks go also to the ACASTI (Association Congolaise pour l'Avancement de la Science, de la Technologie et de l'Industrie) autorities

for inviting me to the research protocol presentation workshop at the University of Kinshasa (2019).

I am grateful to Professors Taba Kalulu and Remy Nsimambote for the proof reading of the thesis. Their suggestions allowed me to improve the quality of the manuscript.

I do not have enough word to express my thanks to my father **Conrad Bayoli Luhala** and my mother **Ernestine Kahindo Luvatsungana** for everything! I am so grateful to my brothers and sisters Jean, Taly, Maidée, Fiston, Konde, Benedicte and Yaya for support. May the parents-in-low Jacques Yoshua and Ogla Mutokambali as well as all the Basua and Jeanne d'Arc Muhesi find here my deep gratitude. I would also like to thank the couple of Professor Vincent Muderwa for their support.

Finally, I thank my wife **Gracia** and our sons **Junias** and **Jaden** who endured and agreed to deprive themselves of many luxuries during the realization of this doctoral thesis. I carry you in my heart. This work is yours!

Contents

List of Figures

List of Tables

List of Acronyms

ABM	:	Agent-Based Model
CSDT	:	Centre de Santé de Diagnostic et de Traitement
CSET	:	College of Science, Engineering and Technology
DFE	:	Disease-Free Equilibrium
DOTS	:	Drug Observed Treatment Short
DPS	:	Division Provinciale de Santé
DRC	:	Democratic Republic of the Congo
DS-TB	:	Drug-Sensitive Tuberculosis
EBM	:	Equation-Based Model
EE	:	Endemic Equilibrium
GAML	:	GAma Modeling Language
GIS	:	Geographic Information System
HHCT	:	Household Contact Tracer
HCM	:	Ho Chi Minh
HIV	:	Human Immunodeficiency Virus
MDR-TB	:	Multidrug-Resistant Tuberculosis
MSLIR	:	Immunized, Susceptible, Latent Infected, Infectious, Recovered
NTP	:	National Tuberculosis Program
ODD	:	Overview, Design concepts, Details
ODE	:	Ordinary Differential Equations
PNLT	:	Programme National de Lutte contre la Tuberculose
Prms	:	Parameters
RK4	:	Runge Kutta 4th
SARS	:	Severe Acute Respiratory Syndrome
SDG	:	Sustainable Development Goals
SEIR	:	Susceptible, Exposed, Infected, Recovered
SIR	:	Susceptible, Infected, Recovered
SNIS	:	Système National d'Information Sanitaire
TB	:	Tuberculosis
WHO	:	World Health Organization

Chapter 1

General introduction

This chapter is the general introduction of this thesis. It is devoted to the presentation of the context of the study, the motivations that led us to carry out this thesis, the research questions, the objectives pursued in the thesis, the methods of investigation, the contribution, and finally the structure of the thesis.

1.1 Context

Systems made of a large number of individuals subject to many environmental variations, interacting with each other and with their environment, such as contamination by an epidemic, transmission and cure, acceptance or rejection of a vaccine against an epidemic: these are complex systems dealt with in this thesis.

The spread of a disease is a dynamic and complex phenomenon. In the world, diseases are often the effects of misery and poverty. To find how to understand epidemiological systems is essential for governments. It is the reason why the modeling-simulation approach is an excellent method as it simplifies reality which is naturally complex. Complex systems are those made of a large number of entities submitted to several environmental variations, which interact between them and with their environment, like a spreading of a disease in a population from a city to others, etc. These complex and dynamical systems can be the scene of emergent "phenomena": Systems which change states can experience sudden transitions, deteriorate or get better. The ability to predict the infection trajectory of a particular disease can help the planning of vaccination production, inpatient treatment, and various other health care initiatives.

1.2 Motivation of the study

The 2018 World Health Organization (WHO) report [Organization et al., 2018a] shows that nearly a third of the world's population is infected with TB, with millions of deaths as well as millions of new cases of infection yearly. This report confirms that TB is one of the top ten causes of death worldwide. For example in 2015, 10.4 million people contracted TB and 1.8 million died from the disease, including 0.4 million among people with HIV (Human Immunodeficiency Virus). Over 95% of TB deaths occur in low- and middle-income countries. Recently, the WHO reports that DRC is one of the 22 countries most infected with TB and is one of the 27 states which supports 85% of estimated number of multi-resistant TB in the world. The report [Organization et al., 2016] confirms that more than 130 000 new cases of TB infection are detected yearly in DRC. We note that in DRC, there is a lot of available data on TB, but it is

very difficult to find a model that uses it and suggests ways to reduce the effects of this infectious disease in the country. Being an African and living in low-income country, it is important to contribute to the control of TB and try to eradicate this disease in our continent by proposing new kind of designing of models and their implementation using real data. This work is a personal contribution to help African governments understand the spread of TB on a large and multi-scale environment.

1.3 Problem statement

In recent years, several models of tuberculosis transmission were presented, but most of them don't keep track of individuals in the population and do not consider the mobility of people in their modeling as one of key factors of the spread of disease. Currently, models of differential equations like SIR and $SEIR$ are the most used, but they are more difficult to apply at the large scale. Formerly, modeling of infectious diseases focused on the contacts of the local networks, i.e the networks in the singular populations (villages, urban centers, localities, regions), a new approach was recently introduced to treat the spread of diseases in a set of populations (local) whose spatial structure and configuration are complex and which are interconnected by the migratory networks of individuals. In ecology, the sets of populations connected and evolving in a multi-patch environment are called metapopulations. Unfortunately, these models can not capture all the behaviors of interacted individuals. These models have increased their weakness with regard to its mobility component, which is treated in an aggregate manner, and therefore do not consider the heterogeneous behaviors of individuals. The agent-based modeling has come to fill this gap, but the complexity of models in terms of multi-scale interactions presents challenges for public health agent-based modeling.

In this thesis, we propose a hybrid way of modeling and simulating complex systems (epidemiological phenomenon) based on mathematical models and intelligent agent-based models. Concrete case studies on the spread of TB in DRC will constitute the implementation of our research.

1.4 Aims and objectives of the thesis

In order to succeed, we set two aims. The first one is to design a new approach that facilitates modeling of infectious diseases using simultaneously mathematics (ordinary differential equations) and artificial intelligence (multi-agent systems). To achieve this aim, the following objectives are set:

- Providing a comprehensive review of literature and characteristics of the tuberculosis spread in the population;
- Designing mathematical and agent-based models;
- Combining the two models and obtain a hybrid model which can benefit simultaneously the advantages of mathematical and agent-based models.

The second one is to assess the question about impact of population mobility on the spread of TB in multi-scale environments. To achieve this goal, we are going:

- To design and propose a virtual multi-scale environment of connected cities;

- To propose the modeling of the dynamics of TB in this environment;
- To produce a tool which can help decision makers to understand the role of population mobility upon the spread of TB in the multi-scale environment;

The obtained result will be valuable for the African ministries of health as well as for health zone managers in the fight against TB in a large and multi-scale environment and the evaluation of the barriers against the evolution of TB in the population. Thus, this thesis is a contribution to the fight against the emergence of diseases in Africa using artificial intelligence (multi-agent systems) and mathematics (Ordinary Differential Equations).

1.5 Methods of investigation

The thesis focuses on the development of simulation methods and techniques. So, models are produced upstream. The thesis is ensured by a close collaboration with all the actors who may possess the needed information for their design, implementation and functioning and by observations and specific surveys put in place to fill any gap. In this research, different methods in applied sciences are used especially mathematical epidemiology, mathematical biology, statistical biology and artificial intelligence, mainly multi-agents system. The model parameters values are essentially taken from the literature and direct discussion with experts in the field of the study framework. Our methodology is summarized in the Fig. 1.1 below:

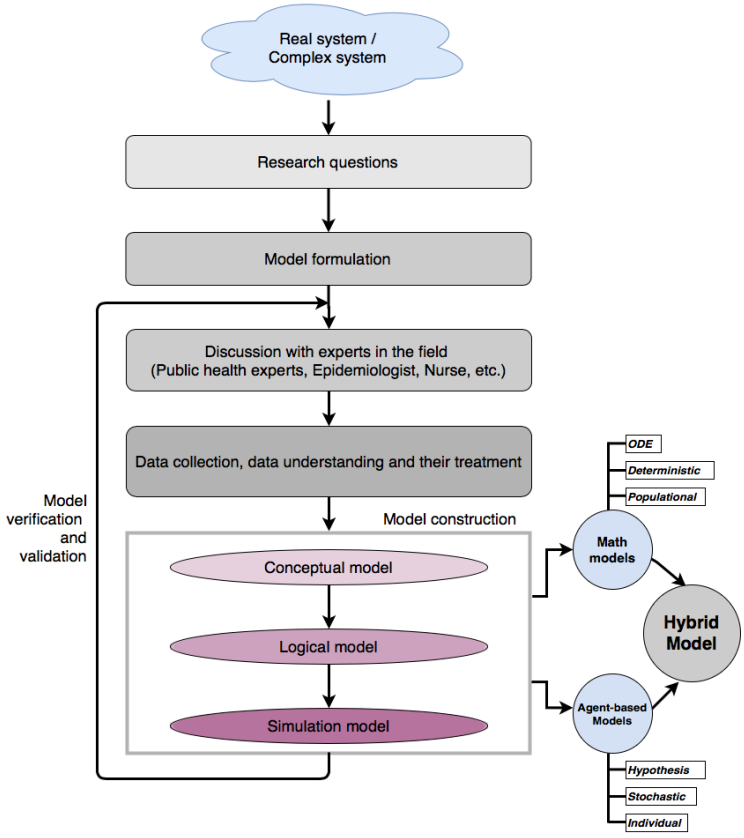


Figure 1.1: Methodology adopted and applied in this thesis

This research is based on real data, their analysis, creation of models and simulation. The available data was provided by the PNLT (Programme National de Lutte contre la Tuberculose: National Tuberculosis Control Program) in Democratic Republic of the Congo. Simulations are made using GAMA platform which allows the modeling and the spatially explicit Agent-Based development. Computer programs are developed in GAML (GAma Modeling Language) [Grignard et al., 2013].

During the development of this thesis, several discussions were held with experts in the field of medicine (lung specialist, public health specialist, etc.) in order to better understand research questions. According to the Fig. 1.1, we note that conceptual model contains the system elements that should be included in our model. The logical model contains logical links between system elements, and the exogenous variables affecting the system (diagram or flowchart). The simulation model consists of representing the logical model using a specialized language. The verification consists of answering the question whether the simulation program really corresponds to the model (notion of correct program) and the validation consists of answering the question whether the model represents reality.

1.6 Contribution of the study

This study is a new framework of modeling infectious disease dynamics in heterogeneous populations. The contribution of this study can be seen in four steps:

- The first one is the literature review of mathematical modeling and agent-based modeling of TB in the population with the given positioning;
- The second one is the proposition of two mathematical models. The first one describes the control of pulmonary TB and the second one focus on evolution and control of drug-sensitive tuberculosis and multidrug-resistant tuberculosis. Their rigorous mathematical analysis and their simulation using real data from the DRC are among the main results provided in this thesis.
- The third one is the proposition of an agent-based model of TB. Designing an environment, modeling the behaviours of agents and the simulation of the model proposed are tasks that have been carried out.
- The fourth and last one is the proposition of a new kind of modeling complex systems by coupling separate models with different formalism in order to obtain a hybrid model that combine both the advantages of EBM (Equation-Based Modeling) and ABM (Agent-Based Modeling) and its application to the spread of TB in a multi-scale environment. This contribution tries to extend new development in mathematical modeling by combining it with Agent-Based Modeling derived from artificial intelligence.

1.7 Outline

This thesis is divided into seven chapters:

- The first one presents the General Introduction. Here, we introduce the problem statement, motivation, research aims and objectives, the methods of investigation used to achieve this thesis, and the contribution of the study.

- The second one deals with the biology and epidemiology of tuberculosis. In this chapter the general situation of TB in the world, Africa and more particularly in the Democratic Republic of the Congo (DRC) is presented. We present also the different means of fight and prevention used in the World and particularly in DRC against TB.
- The third one presents the literature review of modeling and simulation of infectious diseases. Here we present Equations-Based Modeling (EBM) by focusing on compartmental models, and we present also Agents-Based modeling (ABM). A section is focussed on the difference between these two modeling approaches. To complete this chapter, we present some EBM and ABM of TB with our personal criticisms and positioning.
- The fourth one focuses on mathematical modeling and simulation of TB in the population. Two mathematical models of TB are proposed, their rigorous mathematical analyses and simulations are provided. The discussion of results obtained is also presented. Some recommendations are provided to the Congolese health system.
- The fifth one is about agent-Based Modeling and simulation of TB in the population. The structure population and network contact used are described according to DRC context. The simulation of the model is carried out. Results obtained are also discussed.
- The sixth one is based on hybrid stochastic modeling that combine EBM and ABM. Application of this novel approach to the spread of tuberculosis in the population is presented and discussed.
- The seventh and last one of this thesis provides the General Conclusion of the study and future works.

Chapter 2

Biology and epidemiology of tuberculosis, and statistics on data from Democratic Republic of the Congo

In this chapter, we present some basic concepts on TB transmission before talking about TB in the world in general and in the Democratic Republic of the Congo in particular. One section is devoted to the treatment of TB while the last one presents and discussed some statistics on TB data collected from the PNLT (Programme National de Lutte contre la Tuberculose) of DRC.

2.1 Introduction

Bisides significant advances in the fight against the emergence of tuberculosis, this disease continues to affect human populations around the world. Tuberculosis is an infectious disease caused by *Mycobacterium* tuberculosis [Bisuta et al., 2018]. It mainly attacks the lungs for pulmonary tuberculosis, but can also affect other organs of the human body, including the central nervous system, the circulatory system, the genital urinary system, bones, joints and even the skin [Organization et al., 2016].

2.2 Tuberculosis transmission

Transmission between individuals depends on several factors such us the number of infected and expelled droplet, the duration of exposure to the risk area, the level of ventilation of the environment and the virulence of the Mycobacterium tuberculosis [PNLT, 2016]. TB mainly attacks the lungs for pulmonary tuberculosis, but can also affect other organs of the human body, including the central nervous system, the circulatory system, the genital urinary system, bones, joints and even skin [PNLT, 2016, Organization et al., 2018c]. This disease is usually asymptomatic in it early stage, an infectious individual can presents symptoms (fever, cough, weight loss, night sweats, and so on) only after many months, this can cause the patient to delay the time of consultation, and result in the transmission of the bacteria to others people. An active TB individual without treatment can infect about 10 to 15 other

people per year [Organization et al., 2018c]. Without appropriate treatment, up to two-thirds of people with tuberculosis will die from the disease [Organization et al., 2018c].

It should be noted that this infectious disease can also spread through the use of non-sterilized utensils (dishes, drinking glasses) of an infected person. In some cases a pregnant woman with active tuberculosis can infect the fetus (vertical transmission) [Cisse et al., 2007]. Only people with active TB can transmit the disease. The latent infected do not transmit it. Transmission from one person to another depends on the number of infected and expelled goulettes, the activity of environmental ventilation, the duration of exposure to the risk of contamination, and the virulence of the Mycobacterium tuberculosis.

The chain of transmission of this disease can still be broken by the isolation (quarantine) of active TB patients and the effective start of antituberculous treatment.

2.3 Tuberculosis in the world

2.3.1 Introduction

Nowadays, TB is considered as a major global public health problem. Globally, the best estimate is that 10 million people (range, 9.0–11.1 million) developed TB disease in 2017: 5.8 million men, 3.2 million women and 1.0 million children. There were cases in all countries and age groups, but overall 90% were adults (aged $\geq$ 15 years), 9% were people living with HIV (72% in Africa) and two thirds were in eight countries: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (5%), Nigeria (4%), Bangladesh (4%) and South Africa (3%). These and 22 other countries in WHO's list of 30 high TB burden countries accounted for 87% of the world's cases. Only 6% of global cases were in the WHO European Region (3%) and WHO Region of the Americas (3%) [Organization et al., 2018a]. Africa, with 11% of the world's population, alone accounts for 25% of the global burden of TB [Organization et al., 2018a]. The incidence of tuberculosis is increasing every year by 6% and the HIV epidemic is the main cause of this increase. It is well known that factors such as endogenous reactivation, the emergence of drug resistance to TB, and the growth of HIV incidence in recent years call for improved control strategies for this deadly disease.

The bacillus of Koch has no borders, but because of the efforts of the rulers and non-governmental organizations, generally financed by the World Fund, the spread of infection and mortality due to tuberculosis have been brought under control in the majority of Western countries during the last half of the last century. However, with the increase in international travel and intercontinental migration, tuberculosis is gaining new ground where it was thought to have disappeared. The Fig. 2.1 describes the TB situation in the world.

2.3.2 Fight against TB in the world

One of the goals of sustainable development is to end the TB epidemic by 2030 around the world. The WHO strategy aims at reducing the number of deaths due to this disease by 90% and its incidence by 80% between 2015 and 2030.

However, data published in 2015 by WHO indicate that the TB epidemic is larger than previously estimated. It is estimated that it kills 1.4 million HIV-negative people [Organization et al., 2016], making it the world's deadliest infectious disease.

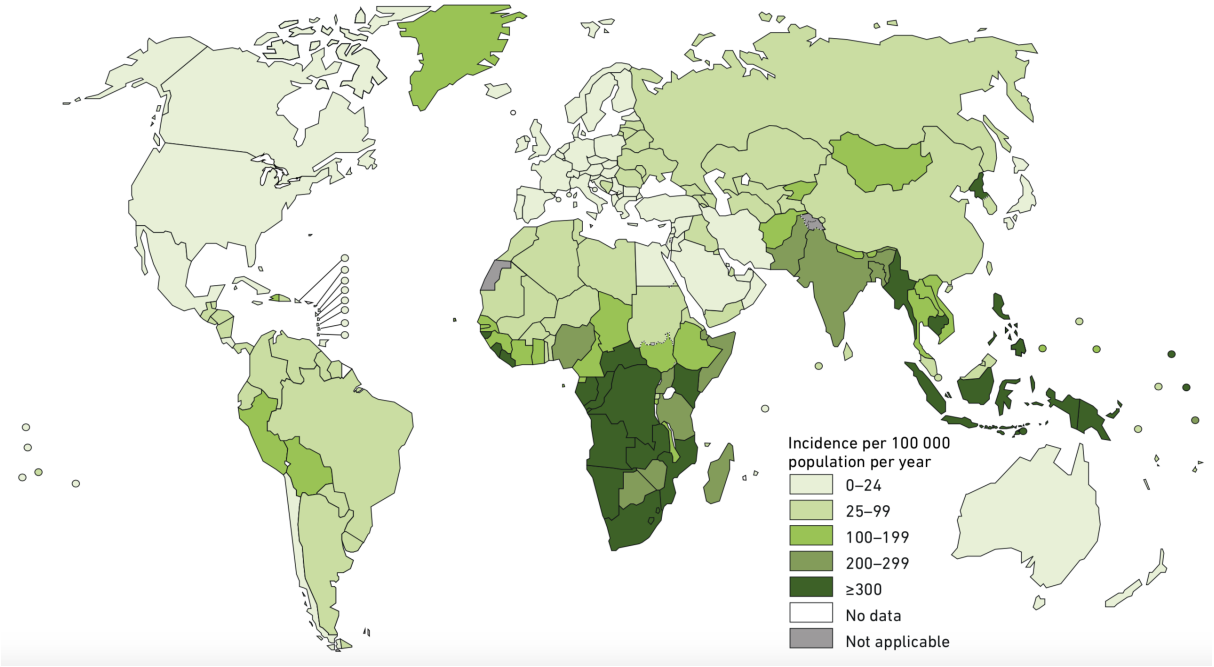


Figure 2.1: TB situation in the world [Organization et al., 2018a]

Overall, progress in the fight against tuberculosis in the world is commendable. Tuberculosis treatment programs around the world have averted 49 million deaths between 2000 and 2015 (including 10 million people living with HIV). In the absence of interventions, this would be over three times higher in 2015.

In Global Fund-supported countries, the mortality related to tuberculosis has decreased by 35% and the actual number of deaths has decreased by 21% between 2000 and 2015 (excluding HIV-positive people). In addition, the number of TB cases in countries where the Global Fund invests has decreased by 5% between 2005 and 2015.

Among the factors that have increased the mortality rate of TB in recent years is Multidrug-resistant tuberculosis (MDR-TB). This MDR-TB is a major public health problem that threatens the considerable progress made in recent years in the care and in prevention of tuberculosis. This is an aspect of antimicrobial-resistant bacteria that do not respond to current medications, limiting treatment options of diseases that would ordinarily be curable [Serge Bisuta, 2018]. Recently, WHO has approved a shorter treatment regimen for multidrug-resistant tuberculosis and a rapid screening test. The Global Fund supports the purchase of new screening technologies and shorter treatment regimens to improve the response to MDR-TB.

The Global Fund provides over 65% of international funding for TB programs. Between 2002 and 2016, disbursed more than USD 5.8 billion for such programs (including programs for co-infection TB / HIV) in more than 100 countries. It focuses on the most affected countries and those with the highest proportion of key populations: people living with TB / HIV co-infection, migrants, refugees and displaced persons, minors, prisoners, children in contact with tuberculosis and injecting drug users in particular [Organization et al., 2016].

Since 2002, 17.4 million people have been treated for laboratory-confirmed pulmonary TB in countries where the Global Fund invests. The number of beneficiaries of tuberculosis screening and treatment

increased by 14% between 2015 and 2016. In addition, 373 000 people are receiving treatment for multidrug-resistant forms of tuberculosis [Serge Bisuta, 2018].

2.4 Tuberculosis in Democratic Republic of the Congo

2.4.1 Introduction

Thirty countries are recognized as carrying the load of more than 85% of the globe including the DRC. For nearly a decade DRC, Nigeria, Ethiopia and the Republic of South Africa are the 4 African countries most affected by cases diagnosed each year according to WHO estimates [Serge Bisuta, 2018]. The disease is commonly associated with poverty. The World Health Organization (WHO) report confirms that over 95% of deaths with TB occur in low- and middle-income countries [Organization et al., 2018a], and the Democratic Republic of the Congo (DRC) is among countries with an estimate incidence of 323 $(209 - 461)$ cases per $100,000$ population, which represents about $250,000$ $(162000 - 357000)$ new cases each year [Bisuta et al., 2018].

DRC is in the three high-burden country lists for TB, TB/HIV and MDR-TB being used by WHO during the period 2016–2020, and their areas of overlap as shown in the Fig. 2.2.

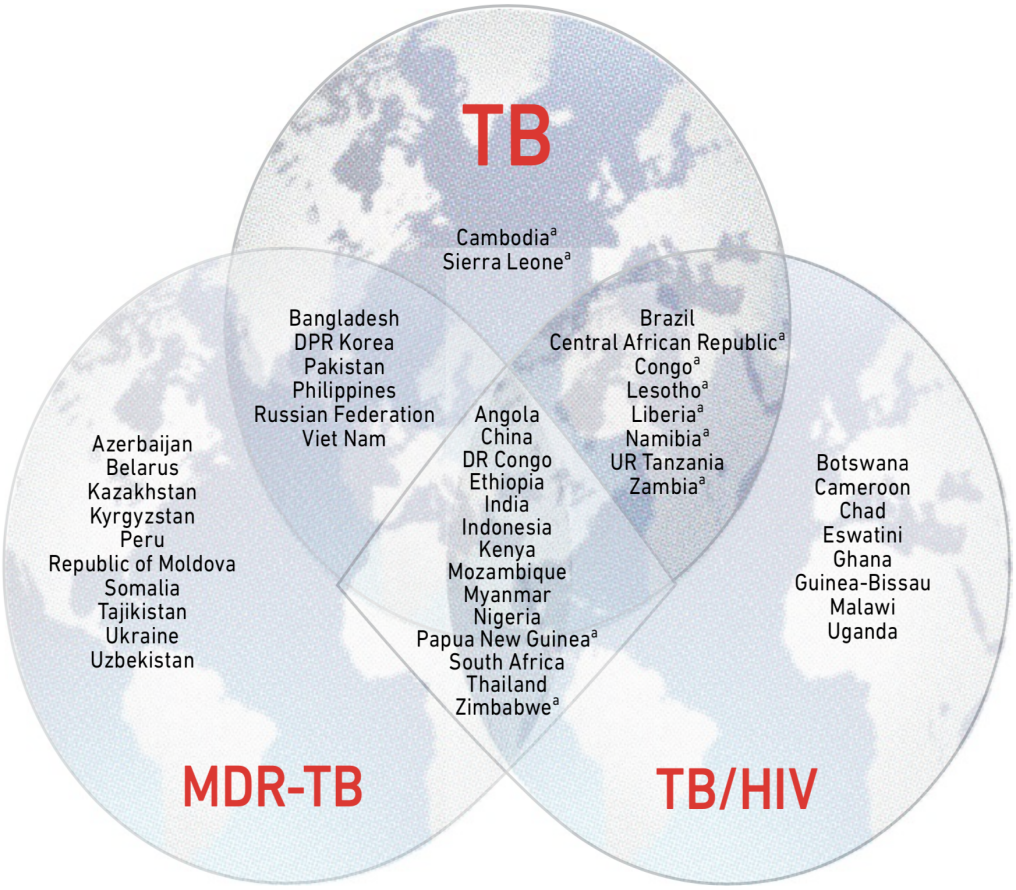


Figure 2.2: The three high-burden country lists for TB, TB/HIV and MDR-TB [Organization et al., 2018a]

DRC is also among the countries with the highest number of TB and HIV coinfected patients [RDC, 2006, Organization et al., 2016]. A multidrug-resistant tuberculosis survey conducted in Kinshasa

/ DRC from 1998-1999 showed a prevalence of 2.2% among new cases of pulmonary tuberculosis with positive microscopy [PNLT, 1999]. Among the hypotheses emitted in this study, non-compliance with the guidelines by health care providers and poor adherence to treatment by TB patients are responsible for multidrug-resistant tuberculosis in Kinshasa; but these lines of thought are still only hypotheses to be confirmed.

2.4.2 Fight against active TB in DRC

In order to carry out the fight against TB, the Congolese government had set up the National Tuberculosis Program named PNLT (Programme National de Lutte Contre la Tuberculose). Currently this program has implemented more than 2000 care structures called Diagnostic Health Center and TB treatment (CSDT: Centre de santé de Diagnostic et de Traitement de la TB), these structures are equipped with microscopes, antituberculous drugs and whose personnel are trained and supervised. All health zones currently in DRC are covered by these CSDTs. Fig. 2.3 presents the TB profile in Democratic Republic of the Congo:

In DRC, patients are diagnosed at the CSDT. Tuberculosis cases diagnosed at the level of the CSDTs are reported to the health zone (operational level), to the DPS (intermediate level) and to the central level (SNIS and PNLT). The CSDT is part of the peripheral level that is to say operational (level of health zone), followed by the provincial level (intermediate) and finally the national level which centralizes reporting [PNLT, 2016].

As DRC is a low income country and therefore did not have enough means, PNLT depends on funding partners, which often a mismatch between available resources and targets. Coverage in management structures needs to be further expanded to serve the entire population, and the mechanism for transporting samples from remote structures to diagnostic centers is the strategy to cover the entire countries (with an area of 2,345 million Km^2). We note that finance is not always present at the right time. For example, in 2015 only 49% of tuberculosis patients were tested for HIV, while every TB patient had to know their status [RDC, 2006].

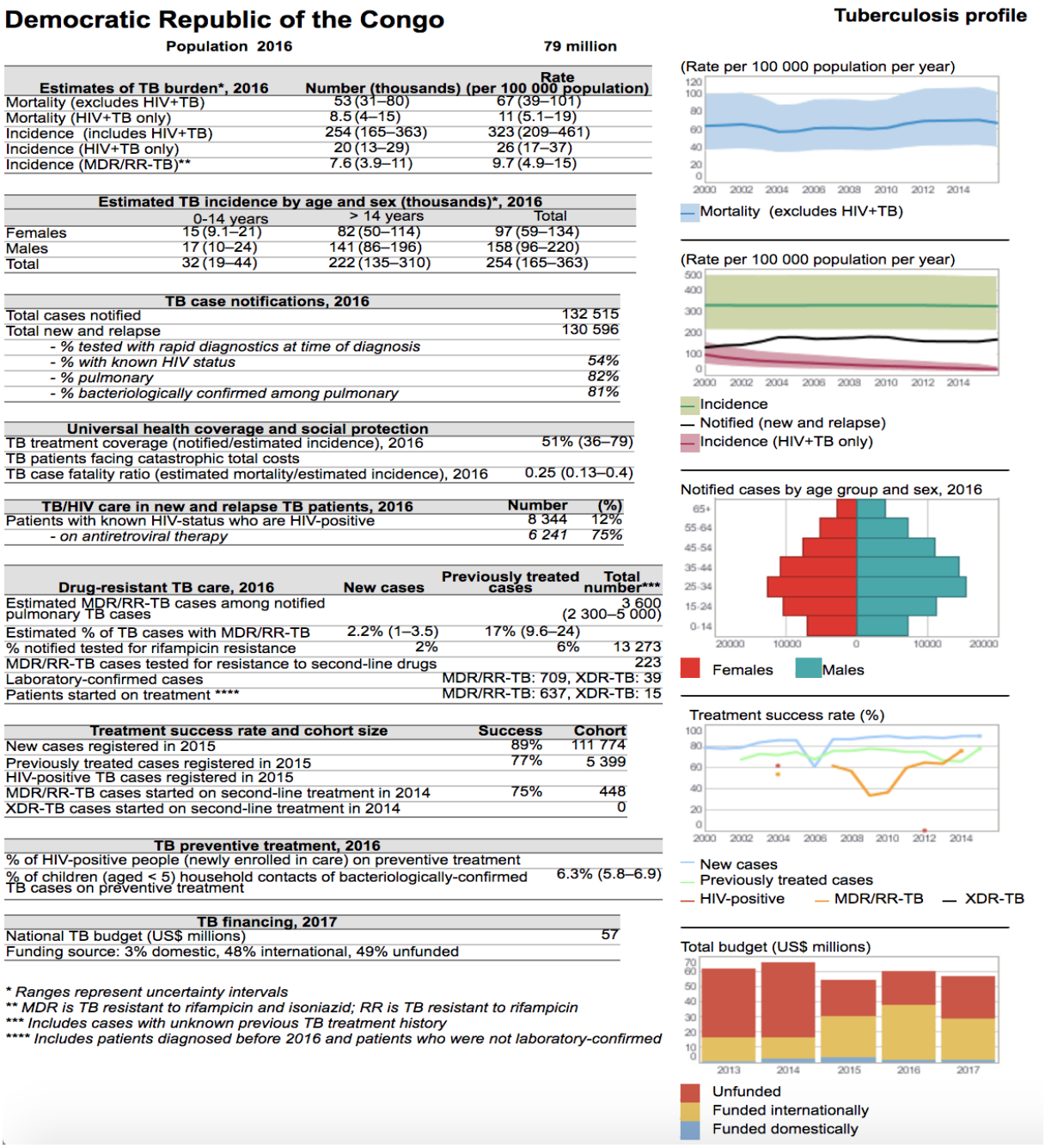
2.5 Treatment of TB

The duration of treatment may be up to eight months for drug-susceptible TB and 20 months or longer for drug-resistant forms, these longer periods may result in loss of livelihood. In the Democratic Republic of the Congo, patients are grouped into three categories and the therapeutic regimes adopted are as follows: category I & III: 2RHZE / 4RH and category II: 2SRHZE / 1RHZE / 5RHE. Taking of drugs is supervised in the first phase by the nurse and in the second phase by a family member or the community (trained and supervised), in the absence of the nurse.

2.6 Statistics on data provided by the PNLT of DRC

2.6.1 Introduction

In this section, we present some statistics on data concerning the trend of tuberculosis in the Democratic Republic of the Congo. These patient data were collected at the national unit of the PNLT (Programme National de Lutte contre la Tuberculose). Concerned period is from 2007 to 2017. These data concern new cases, relapses, treatment failures and treatment resumptions. Some analyses were based on sex



Democratic Republic of the Congo — **Tuberculosis profile**

Population 2016: 79 million

Estimates of TB burden*, 2016	Number (thousands)	Rate (per 100 000 population)
Mortality (excludes HIV+TB)	53 (31–80)	67 (39–101)
Mortality (HIV+TB only)	8.5 (4–15)	11 (5.1–19)
Incidence (includes HIV+TB)	254 (165–363)	323 (209–461)
Incidence (HIV+TB only)	20 (13–29)	26 (17–37)
Incidence (MDR/RR-TB)**	7.6 (3.9–11)	9.7 (4.9–15)

(Rate per 100 000 population per year)

Mortality (excludes HIV+TB)

Estimated TB incidence by age and sex (thousands)*, 2016	0-14 years	> 14 years	Total
Females	15 (9.1–21)	82 (50–114)	97 (59–134)
Males	17 (10–24)	141 (86–196)	158 (96–220)
Total	32 (19–44)	222 (135–310)	254 (165–363)

(Rate per 100 000 population per year)

Incidence
Notified (new and relapse)
Incidence (HIV+TB only)

TB case notifications, 2016	
Total cases notified	132 515
Total new and relapse	130 596
- % tested with rapid diagnostics at time of diagnosis	
- % with known HIV status	*54%*
- % pulmonary	*82%*
- % bacteriologically confirmed among pulmonary	*81%*

Universal health coverage and social protection	
TB treatment coverage (notified/estimated incidence), 2016	51% (36–79)
TB patients facing catastrophic total costs	
TB case fatality ratio (estimated mortality/estimated incidence), 2016	0.25 (0.13–0.4)

TB/HIV care in new and relapse TB patients, 2016	Number	(%)
Patients with known HIV-status who are HIV-positive	8 344	12%
- on antiretroviral therapy	*6 241*	*75%*

Notified cases by age group and sex, 2016

Females Males

Drug-resistant TB care, 2016	New cases	Previously treated cases	Total number***
Estimated MDR/RR-TB cases among notified pulmonary TB cases			3 600 (2 300–5 000)
Estimated % of TB cases with MDR/RR-TB	2.2% (1–3.5)	17% (9.6–24)	
% notified tested for rifampicin resistance	2%	6%	13 273
MDR/RR-TB cases tested for resistance to second-line drugs			223
Laboratory-confirmed cases		MDR/RR-TB: 709, XDR-TB: 39	
Patients started on treatment ****		MDR/RR-TB: 637, XDR-TB: 15	

Treatment success rate (%)

New cases
Previously treated cases
HIV-positive MDR/RR-TB XDR-TB

Treatment success rate and cohort size	Success	Cohort
New cases registered in 2015	89%	111 774
Previously treated cases registered in 2015	77%	5 399
HIV-positive TB cases registered in 2015		
MDR/RR-TB cases started on second-line treatment in 2014	75%	448
XDR-TB cases started on second-line treatment in 2014		0

TB preventive treatment, 2016	
% of HIV-positive people (newly enrolled in care) on preventive treatment	
% of children (aged < 5) household contacts of bacteriologically-confirmed TB cases on preventive treatment	6.3% (5.8–6.9)

TB financing, 2017	
National TB budget (US$ millions)	57
Funding source: 3% domestic, 48% international, 49% unfunded	

Total budget (US$ millions)

Unfunded
Funded internationally
Funded domestically

** Ranges represent uncertainty intervals*
*** MDR is TB resistant to rifampicin and isoniazid; RR is TB resistant to rifampicin*
**** Includes cases with unknown previous TB treatment history*
***** Includes patients diagnosed before 2016 and patients who were not laboratory-confirmed*

Figure 2.3: TB Profile for Democratic Republic of the Congo [Organization et al., 2018a]

and age of individuals in relation to the new case. We used the programming languages python and R to perform some statistics on these data.

2.6.2 New cases

New cases are patients who have never received TB treatment (or for less than a month) at the time of diagnosis. Tab. 2.1 below shows new case per province and per year:

Based on results presented in the Tab. 2.1, it seems that DRC is one of the most affected countries by tuberculosis in the world and more particularly in Africa. The province of KATANGA ranks as the

Table 2.1: New cases of TB in DRC per year and per province

Health zone	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
BAS-CONGO	3304	3225	3327	3231	3135	3183	2944	2848	2892	3070	3144
BANDUNDU	5969	7056	6258	8314	7860	7631	7867	8921	8882	8993	9754
EQUATEUR	5523	5583	6007	6314	6781	6031	6124	7430	6288	7420	10590
KASAI-OCC.	6008	7011	7815	7960	8470	8565	8087	7259	7506	8030	7825
KASAI-OR.	7641	7961	7671	9367	7472	7915	8131	8087	8771	9800	11614
KATANGA	14124	14786	16915	13089	13021	12256	13875	13904	14242	14690	16539
KINSHASA	9147	9531	9306	9274	8807	9119	8887	9433	9730	10146	11126
MANIEMA	2540	2399	2631	2495	2284	2295	2197	2398	2108	2218	2564
NORD-KIVU	2699	2809	3155	3014	2963	3062	3055	3053	3331	3885	4441
SUD-KIVU	2370	2426	2461	2471	3099	3429	2803	3301	3482	3758	4320
PROVINCE-OR.	6774	6778	7645	8124	7429	7638	7556	8997	9439	10377	11638

province with the highest number of new cases from 2007 to 2017. The year 2017 is positioned as a year in which there were more new cases in almost all provinces with the exception of BAS-CONGO and KASAI-OCCIDENTAL.

Table 2.2: Average of new cases of TB in DRC per year

Year	Average
2007	5783.58
2008	6065.83
2009	6376.50
2010	6407.00
2011	6204.67
2012	6192.25
2013	6205.83
2014	6539.92
2015	6630.25
2016	6868.08
2017	8058.25

Based on the Tab. 2.2, results confirm that the average number of new TB cases per province is increasing yearly.

Resullts presented in Fig. 2.4 show that the average of new cases was less than 6000 per province in 2007, but has risen to over 8000 by 2017. This represents an increase of almost 50% over a period of 11 years. This proves the weakness of the current health system in DRC, which is unable to reduce the incidence of TB in the population.

2.6.3 Relapses

Relapses are patients who have already been treated and have been cured or have completed treatment and return with new bacteriological confirmation. Tab. 2.3 shows relapse individuals from 2007 to 2017 per province and per province.

The results obtained in Tab. 2.3 show that KINSHASA has more relapses followed by the KATANGA province. MANIEMA province has few relapses compared to all provinces for the year 2017.

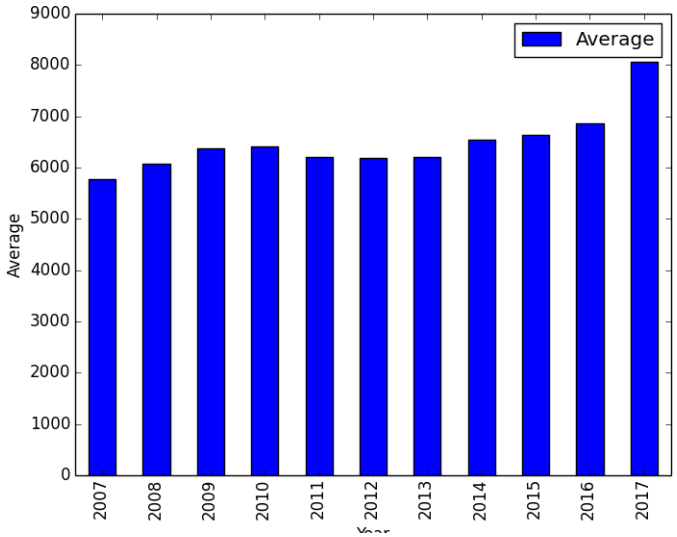


Figure 2.4: Average of TB new cases per year in DRC

Table 2.3: Relapse per year and per province

Health zone	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**
BAS CONGO	243	205	248	203	175	204	207	248	213	229	268
BANDUNDU	230	280	213	265	260	247	252	230	239	236	271
EQUATEUR	288	271	262	231	224	214	189	231	208	231	293
KASAI OCC.	320	307	351	358	352	363	332	362	300	313	245
KASAI OR.	485	500	567	625	468	545	587	613	708	651	843
KATANGA	644	533	751	593	515	507	576	584	624	666	663
KINSHASA	1219	1327	1342	1225	1180	1328	1184	1341	1263	1366	1496
MANIEMA	101	80	104	94	100	104	103	74	103	96	87
NORD KIVU	85	71	100	84	85	98	94	88	104	122	152
SUD KIVU	151	127	153	138	127	94	129	140	142	167	156
PROVINCE OR.	240	302	292	322	275	273	328	387	431	483	487

Tab. 2.4 reveals that the year 2017 is positioned as the year in which there were many relapses in the Democratic Republic of the Congo with an average of 451 persons.

As shown in Fig. 2.5, results show that relapses increased by more than 25% over 11 years. During the year 2017 there were many relapses. These individuals therefore constitute a new reservoir of the disease because these individuals can transmit the disease. The Congolese government will have to provide a mechanism for monitoring cured patients to avoid a large number of relapses. It important to mention that since DRC is poor and access to provinces is difficult due to lack of roads, it is sometimes difficult to reach all the sick. In addition to these efforts, the Congolese government should facilitate access to medicines in isolated provinces. This will enable all patients to have access to treatment

Table 2.4: Average per year of relapse patients.

Year	Average
2007	364.182
2008	363.909
2009	398.455
2010	376.182
2011	341.909
2012	361.545
2013	361.909
2014	390.727
2015	394.091
2016	414.545
2017	451.000

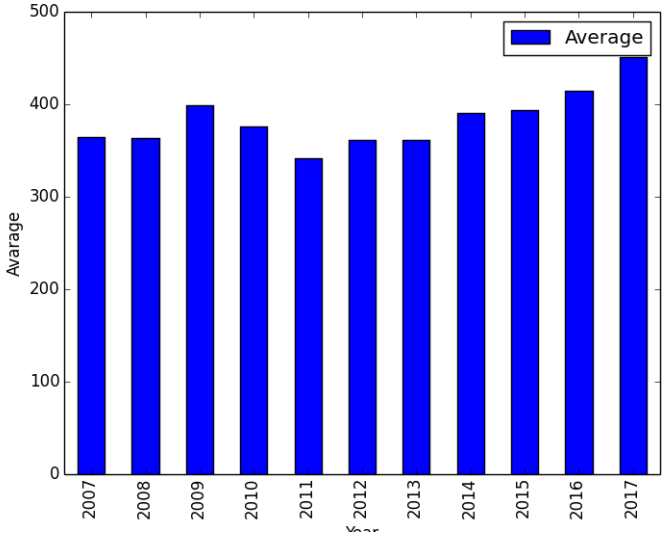


Figure 2.5: Average of TB relapse patients from 2007 to 2017 in Democratic Republic of the Congo.

2.6.4 Treatment failures

Failures are patients who have maintained a positive bacilloscopy beyond the 5th month of treatment. Tab. 2.5 presents all treatment failures from 2007 to 2017 per province.

Based on the results in the Tab 2.5, there is less treatment failure in almost all provinces. These results show that theurapic success has reached a good percentage in DRC. The provinces KATANGA, KINSHASA and PROVINCE-ORIENTAL presented more treatment failures compared to others.

Results obtained in Tab. 2.6 gives a clear improvement of about 50% from 2007 to 2017 in the therapeutic process.

Results presented in Fig. 2.6 show that there are fewer TB treatment failures in DRC from 2007 to 2017. Indeed, over 11 years the average number of treatment failures has fallen by more than 50%. This proves the effectiveness of the drugs used and management.

Table 2.5: TB treatment failure per province from 2007 to 2017.

Health zone	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
BAS CONGO	55	33	50	28	23	39	34	35	37	30	17
BANDUNDU	61	48	47	45	40	24	40	29	36	21	12
EQUATEUR	68	45	53	47	39	52	32	28	33	22	19
KASAI OCC.	81	50	53	34	21	23	18	15	10	5	3
KASAI OR.	115	93	108	81	60	51	54	42	42	41	34
KATANGA	195	151	160	135	119	114	149	132	152	145	241
KINSHASA	178	164	149	140	117	141	99	78	73	114	75
MANIEMA	29	20	14	13	7	10	15	7	9	14	4
NORD KIVU	43	45	63	49	35	40	40	49	54	42	56
SUD KIVU	55	34	33	23	24	33	28	18	14	21	17
PROVINCE OR.	120	108	116	118	88	70	59	71	57	62	45

Table 2.6: Average per year of treatment failure.

Year	Average
2007	90.9091
2008	71.9091
2009	76.9091
2010	64.8182
2011	52.0909
2012	54.2727
2013	51.6364
2014	45.8182
2015	47.000
2016	47.000
2017	47.5455

2.6.5 Treatment resumptions

This group represents patients who have stopped taking the drug for more than 2 months and return with a positive smear test. Tab. 2.7 shows the resumption of TB treatment per province from 2007 to 2017 in DRC.

Among the patients, there are those who decided by themselves to stop their treatment and come back to continue because the germ has been reactivated. Tab. 2.7 shows that PROVINCE ORIENTAL and KINSHASA presented many cases of TB resumption from 2007 to 2017 in DRC.

Tab 2.8 show that the number of these patients decreased each year in DRC. Fig. 2.7 shows the average by province of patients who resumed treatment.

Results obtained in Fig. 2.7 show that from 2007 to 2017 the number of these patients decreased by more than 50%. This proves that patient management has improved further.

2.6.6 Age and gender consideration

By considering gender, we obtain the results presented in Tab. 2.9 below.

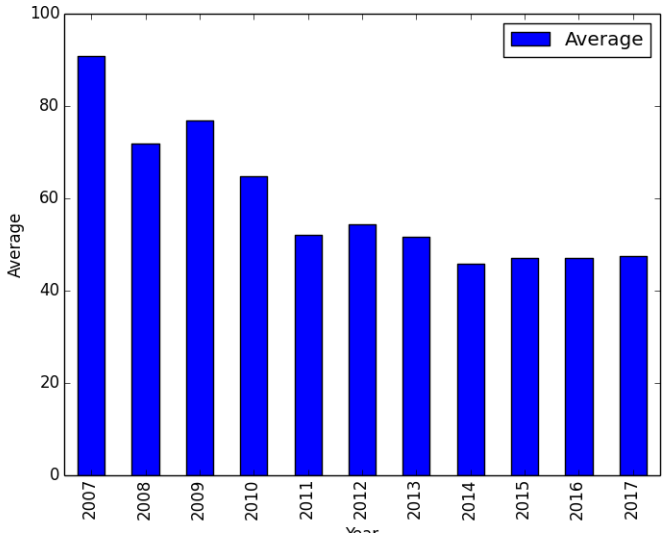


Figure 2.6: Average of patients whose treatment failed after 5 months of treatment from 2007 to 2017 in Democratic Republic of the Congo.

Table 2.7: Treatment resumption per province from 2007 to 2017

Health zone	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**
BAS CONGO	50	41	33	24	20	19	18	20	20	29	23
BANDUNDU	47	18	27	19	13	23	29	21	28	8	7
EQUATEUR	69	60	80	67	72	52	44	45	45	29	12
KASAI OCC.	69	66	51	43	32	38	40	42	23	5	0
KASAI OR.	148	140	139	155	93	97	65	59	79	35	21
KATANGA	77	76	110	101	45	63	109	85	89	155	131
KINSHASA	146	107	96	89	65	67	92	98	84	0	68
MANIEMA	27	16	14	12	17	19	10	15	8	4	0
NORD KIVU	53	76	46	45	39	32	40	35	37	40	51
SUD KIVU	68	54	50	43	51	56	43	59	43	15	12
PROVINCE OR.	167	119	137	198	140	131	106	116	91	53	62

Fig. 2.8 presents the maximum of TB new cases by gender from 2007 to 2017 in Democratic Republic of the Congo.

By considering age and gender of patients, the results obtained in Fig. 2.8 show that men are the most affected by TB in DRC. By considering age, we obtain the results presented in Fig. 2.9.

The Fig. 2.9 shows that the most affected age group is 25 to 34 years old (youth). We encourage the Congolese health system to disseminate knowledge about TB to young people. For example, the government can focus on advertisements about the harms of TB and encourage young people to agree to be screened free of charge.

Table 2.8: Average per year of patients who resumed treatment

Year	Average
2007	83.7273
2008	70.2727
2009	71.1818
2010	72.3636
2011	53.3636
2012	54.2727
2013	54.1818
2014	54.0909
2015	49.7273
2016	33.9091
2017	35.1818

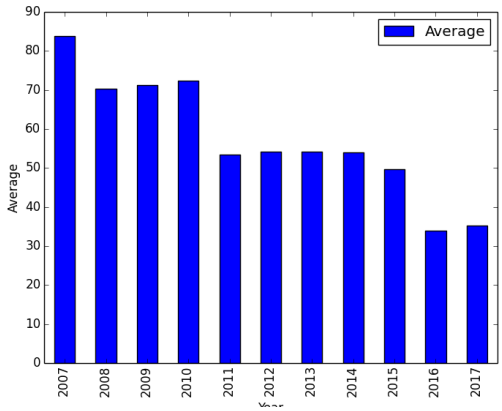


Figure 2.7: Average by province concerning patients who resumed treatment from 2007 to 2017 in Democratic Republic of the Congo.

Table 2.9: TB new cases by gender in all provinces from 2007 to 2017 in RDC

Year	Male	Female
2007	35195	30904
2008	37171	32485
2009	37848	32641
2010	40124	33529
2011	38933	32388
2012	39937	31187
2013	40098	31122
2014	42735	32604
2015	44231	32401
2016	47175	34383
2017	54131	39636

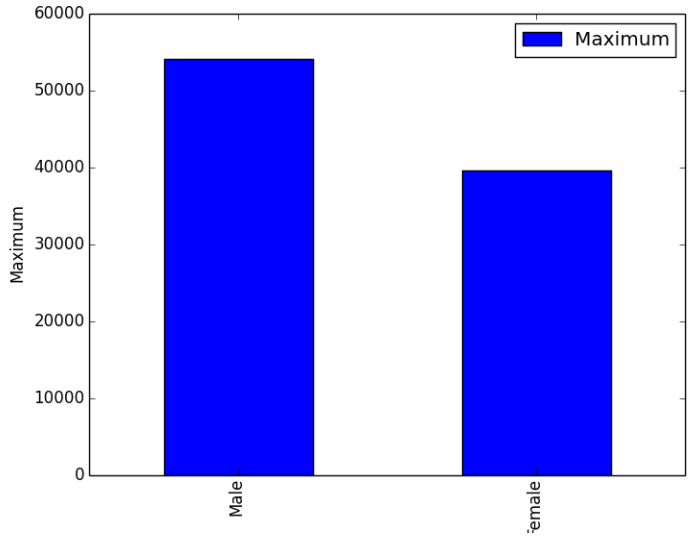
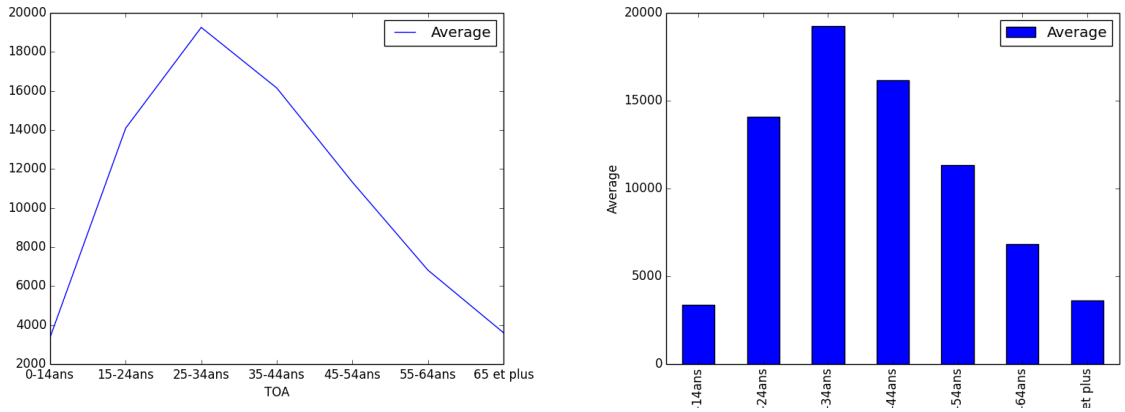


Figure 2.8: Maximum of TB new case by gender.



(a) (b)

Figure 2.9: Maximum of new case by age from 2007 to 2017 (a) and (b) in Democratic Republic of the Congo.

2.7 Conclusion and Positioning

Tuberculosis is both a cause and a consequence of poverty. The disease spreads quickly in areas where living conditions are precarious. Even when free treatment is available, patients have to bear costs such as those related to their travel and good nutrition, essential to keep their shape.

To end global TB and combat new threats to global health security, the Global Fund must be able to reach the most vulnerable people, wherever they are, to provide them with prevention and treatment services.

The unprecedented numbers of people displaced around the world as a result of conflict, poverty, persecution or epidemic outbreaks are representative of the challenges of providing health care to vulnerable populations in difficult response contexts. Fragile health systems are overburdened or even destroyed when a country or region is faced with an epidemic outbreak, natural disaster, armed conflict or

fragile governance, and this often results in poor health and access to inequitable care.

As Africa is the most affected continent with TB, and particularly the DRC which is one of the underdeveloped countries most affected by the rapid progression of this disease despite the efforts of the central government, it is crucial that in parallel with the efforts of the Global Fund, African researchers in mathematics, bio-statistics, computer science and epidemiology continue to work together to develop models that will help to control this disease.

Based on results presented in Section 2.6, it is clear that the Congolese government still has a long way to go to control TB in the country. As researchers, we have a responsibility to work with the government to ensure that this disease will be controlled in the future. This will allow DRC to effectively align itself with the TB halt strategy for its elimination in 2030 in line with the objectives of Sustainable Development Goals (SDG).

In the next chapter, we present the literature review on modeling and simulation of infectious diseases in the population. Mathematical modeling and agent-based modeling are presented and compared. Some related works are also presented and discussed with positioning.

Chapter 3

Literature review on modeling and simulation of infectious diseases in the population

This chapter displays a literature review on modeling and simulation of the dynamics infectious diseases. For that the chapter introduces mathematical modeling and agent-based modeling of the spread of epidemics in the population. Before that, we try to explain the difference between complex and complicated system. One section is also devoted to the fundamentals of computer simulation. Some related works of agent-based models and equation-based models of tuberculosis are also presented in this chapter.

3.1 Introduction

It is sometimes difficult or impossible for theoretical or ethical reasons to carry out real studies on human. The establishment of theoretical models allows to complete knowledge, sometimes imperfect, on the characteristics of a disease, to produce its future development and to determine its character if certain character of environment or people change. Compared to a biological model, the replica of reality, scales and theoretical model materials change. It is about the mathematical or computer representation that replaces the role of model, describing and explaining what is happening or what could happen if conditions change in reality. To represent a reality, we will be called to produce models.

3.2 Definition of terms

3.2.1 Model

A model is a mathematical, or graphic and computerized representation of the objects and the relations between them in a confined zone of the real world [Wooldridge and Jennings, 1994]. A model can also be viewed as a simplified representation of a complex reality. To be useful, models must be adapted to their objects and be conveniently studied and validated [Ferber and Weiss, 1999].

3.2.2 System

In [Dori and Sillitto, 2017] a system is defined as a set of interacting or interdependent component parts forming a complex whole. Every system is defined by its spatial and temporal boundaries, surrounded and influenced by its environment, described by its structure and purpose and expressed in its functioning.

3.2.3 Modeling - simulation

Modeling – simulation, first of all, consist in the designing of a model. It is a way of making explicit the complexity of a system in order to better understand its functioning and to make good decisions. It brings the complex system to be experiment without altering it too much, often difficult in real life situations [Kasereka et al., 2014, Kasereka et al., 2018a]. It enables the system to be accessible at the level of its structure (description) and of its functioning; it tests hypotheses put up (validation), to have new hypotheses (discovery), and predict its functioning if its structure is changed (prediction). Modeling consists both to identify and formulate some problems by constructing models and seeks to solve these problems reasoning by simulations. Modeling process can be described schematically by distinguishing the following three stages: (1) the development of a model from the real world, (2) the functioning of the model itself within mathematics, and (3) the comparison of the results of the model with the real world [Duperret, 2016]. At each stage of modeling and simulation process, it is necessary to answer some questions in order to make the study intelligible in itself and to make the simulation results reproducible. So, the modeling activity requires [Quesnel, 2006]:

- To define the questions asked for the real phenomenon;
- To define studied system: the elements of the real phenomenon to be taken into account, their relations, all according to the question asked;
- To establish an experimental plan;
- To adopt a paradigm and formalism (or more) for making the model a reality;
- To simulate the model according to the experimental plan;
- To analyze the simulation obtained results.

Below in Fig. 3.1 we present an illustration of modeling - simulation process:

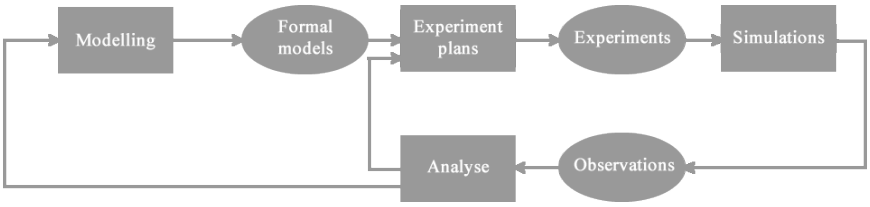


Figure 3.1: Illustration of modeling - simulation process [Quesnel, 2006]

Modeling is a tool often used to facilitate the evaluation of disease management activities. It is a way to explain complexity of system in order to better understand how it works and make the right decisions [Keeling and Rohani, 2011].

3.3 Complex systems

3.3.1 Definition

Several references attempt to define complex systems. A system is complex when it is made of a large number of differentiated autonomous components that interact among them in a non-trivial way. This system is also characterized by the emergence at the global level of new properties, not observable at the level of components system and by a global operating dynamic difficult to predict from the observation of the constituents and their elementary interactions.

The complexity is closely related to the non-linear character of equations that govern the dynamics of the complex system with a very large number of degrees of freedom where the collective behavior of the agent systems resulting from their interactions and dynamics (which can be in continuous or discrete time, sequential or simultaneous entities), that is infinitely richer than the individual behavior of the agents that compose it.

Based on these different definitions, we can list common properties of most complex systems:

- The complex system is made of a large number of elements;
- Often the elements are several types and have an internal structure that cannot be neglected;
- The elements are connected by nonlinear interactions, often of different types;
- The system is subject to external influences at different scales.

The main characteristic of a complex system is the existence of feed-backs of collective behaviors and emergent (macroscopic) properties on the behavior of (microscopic) elements. In fact, the elements will collectively modify their environment, which will constrain them and modify their possible states or behaviors. In a complex system, to know the properties and behavior of isolated elements is not enough to predict the global behavior of the system.

The epistemological references have given rise to a new definition of a complex system. It is a system built by the observer who is interested in it. Complexity being represented by an entanglement of inter-relationships interactions; the system is represented as an intelligible and finite interweaving of interrelated actions [Simplixi, 2013].

3.3.2 Complex vs. complicated

The term complex is used when it is difficult to display the totality of information, to list the totality of interactions or to understand the multitude of the factors which influence the system. If we have some number of information at least one of them is unknown to us, which we do not understand or that last does not allow us to find the solution instantly and / or to understand the link with others, we can say that it is a complex system.

Fig. 3.2 attempts to illustrate the difference between simple, complicated and complex system.

We will say that a problem is simple when it's easy, a problem that's the comprehension is immediate, spontaneous and traducible by an appropriation of the information individually and collectively. A problem is complicated when it's not easy, so it's difficult, but we still manage to solve it. In this sense,

Figure 3.2: Illustration of the difference between simple, complicated and complex [Simplixi, 2013]

we are called to accomplish by step process to understand and appropriate all the factors that influence itself and form a whole. The understanding of this type of problem is progressive [Simplixi, 2013].

A problem is complex when its understanding is partial. It requires the use of modeling and simulation techniques to help us to identify it. For example, we can confirm that the human body is complex because it's a set of a multitude of different components in interaction. We can cite cells, tissues, water, neurons, etc. but we cannot know how all these components interact. For example, it is complex to explain how works an ant colony in an anthill because we don't understand all the factors that come into account and interact between them.

Nowaday, human has not yet acquired the capacity to spontaneously understand a complexity; he must first model and simulate it to try to identify it. By cons, when it's complicated, we have the ability to find solution which is, indeed, a set of simple things. To understand it, we must first decompose and isolate each of the elements and then be able to reassemble them. The relationship between cause and effect requires analysis or other form of investigation and / or application of knowledge coming from an expert.

3.3.3 Complex systems theory in epidemiology

The spread of an infectious disease is a dynamic and complex phenomenon. In fact, an infectious disease evolves over time and spreads in a population located in a given geographical region. This epidemiological phenomenon involves a very large number of components such as the host, the vector, the pathogen, the risk factors, the level of protection, etc. whose interactions give rise to the emergence of events (new cases for example) that can be located at different levels of spatial and temporal scales. These particularities make an epidemiological phenomenon be qualified as a complex system and can therefore be modeled as a process to define it [Arnaud, 1991, Waldvogel et al., 2012].

Considering a disease that is spread in a given population, a person is the subject of internal processes when he is infected, but also subject of external processes because this person is infected by a disease spreading in a given environment. These interactions between several entities that are difficult to define without going through a modeling prove that epidemiological phenomenon is a complex system.

3.4 Mathematical Modeling of infectious diseases

3.4.1 Introduction

The dynamics of a disease in a population is not easy to understand. So, the numbers of healthy and sick individuals evolve over time. A healthy individual can pass several states: susceptible, infectious, recovered, etc. such a phenomenon can be studied by modeling it by differential equations and by

determining its behavior through the numerical resolution of these equations [Kasereka et al., 2014, Ndondo Mboma, 2017].

3.4.2 Compartmental models

Several compartmental models have been applied to simulate epidemiological phenomena. The principle of these models is that the individuals of a population are distributed into several groups or compartments as being a homogeneous structure [Diekmann and Heesterbeek, 2000]. For example, considering any disease, there may be compartments named Susceptible (S) that contains individuals susceptible to be infected or healthy, Exposed or Infected (E) that contains infected individuals but that cannot contaminate others, Infectious (I) that contains sick persons and able to contaminate others, Recovered (R) which contains the individuals who are immunized.

Compartmental models have been used for years. The Kermack and Mac Kendrick model is one of those models on which current models are based [Goufo et al., 2014]. There are several mathematical models used in the field of epidemiology such as SI, SIR, $SEIR$, etc. The main idea of all these models is the same but only the existence of the other compartments makes them different from each other. The basic idea is to divide the total population into several states according to the nature of the disease and its effects in the environment. But the distribution must be based on the constraints of proportionality. For example, the force of infection must be proportional to the portion of sick people in the population. Therefore, proportionality rates are very necessary for each compartment to form an equation to simulate the compartment variable.

In the following lines, we present some existing compartmental models.

The SI compartmental model

We consider a disease that is transmitted directly from one member of a given population to another in a short time in order that births and "natural" deaths have a negligible impact on the dynamics of disease. The fraction of the population that is healthy but potentially infected with the disease is called susceptible and the compartment containing these individuals is labeled S. In a given time t, the compartment S contain $S(t)$ individuals. In the same way, people who are afflicted by the disease are classified as infected. The compartment containing this fraction of population will be noted I and contain $I(t)$ individuals at a given time t [Anderson and May, 1992]. Now, we consider that the probability that a susceptible individual will become infected is proportional to the number of individuals currently infected and that the proportionality coefficient is $i \geq 0$. If a large number of people are involved, it is expected that one of them will become newly infected each day. In the form of differential equations, the model can be noted as the system 3.1:

$$\begin{cases} \frac{dS}{dt} = -iIS \\ \frac{dI}{dt} = iIS \\ N = S + I \end{cases} \tag{3.1}$$

For many diseases, healing is fortunately possible. If, at each unit of time, an infected individual has the probability g of "curing" the disease and becoming susceptible again, we have on average (within the same limits as above) individuals who recover every day. The system of equations thus becomes as noted in system 3.2:

$$\begin{cases} \frac{dS}{dt} = -iIS + gI \\ \frac{dI}{dt} = iIS - gI \\ N = S + I \end{cases} \tag{3.2}$$

And we refer to it as a SIS model. This model is apply in [Leon et al., 2017].

The SIR compartmental model

SIR is a dynamic model that allows describing of the state of a system and the evolution of a set of variables at a given time. This description is based on the solutions obtained by solving differential equation. In this model, S refers to healthy individuals (or those who are susceptible to infection) in the concerned population, I refer to those who are Infectious (able to infect others), and R those who are recovered and can no longer be infected, under the assumption that a cured individual is definitively immunized. The size of each of these populations is variable in time, which can be modeled by a function of the independent variable t, the time: $S(t)$, $I(t)$ and $R(t)$.

If, during the spread of the epidemic, the number N of the total population can be considered constant, we write:

$N = S(t) + I(t) + R(t)$

This system can be represented graphically as in Fig. 3.3 below:

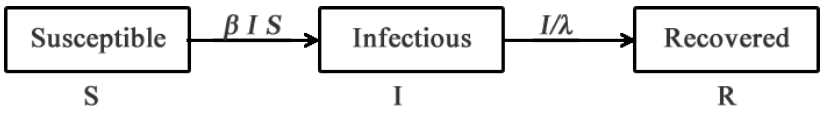


Figure 3.3: Illustration of the SIR compartmental model [Kasereka et al., 2014]

With:

- S: the portion of healthy people
- I: the portion of infectious persons
- β: the rate of incidence or contact
- $\frac{1}{\lambda}$: the cure rate

As illustrated in Fig. 3.3, each compartment is associated with a state variable: S, I and R.

It is about to write a system of differential equations which links the derivative of the functions, $\frac{dS(t)}{dt}$, $\frac{dI(t)}{dt}$ and $\frac{dR(t)}{dt}$, to the functions themselves, $S(t)$, $I(t)$ and $R(t)$. The values of S, I and R are always positive and dimensionless. The spread of the epidemic results from contaminant contacts between infected people and healthy people. In this model, the number of infected increases with the number of contaminant contacts between infected and healthy individuals. This number is proportional to the effective of infected and healthy population. So, the product of these two populations I and S. Thus, we can write:

$$\frac{dI(t)}{dt} = \beta IS \tag{3.3}$$

The parameter $\beta < 0$, called the incidence rate, could be written in the form of a product of two parameters. The value of the first reports the proportion of actual contacts between a healthy and an infected person i, among all those possible during a time interval dt, that is $I(t)S(t)$ (this parameter is related to the density of population, for example). The value of the second parameter reports the probability that such contact transmits the disease of the infected person to the healthy person (probability depends on the virulence of the infectious agent). The effective of the healthy population decreases symmetrically. From this, we can write:

$$\frac{dS(t)}{dt} = -\beta IS \tag{3.4}$$

If an individual remains sick on mean λ days, then $\frac{I}{\lambda}$ is, at any moment, the measure of the flow of individuals who heal, then leave the compartment I, come accumulate in the recovered compartment R and cannot be infected because they are immune. The differential equation that governs the evolution of the number of infected is then written:

$$\frac{dR(t)}{dt} = \frac{I}{\lambda} \tag{3.5}$$

The set of all equations presented above forms a system of differential equations that we note as follows:

$$\begin{cases} \frac{dS}{dt} = -\beta IS \\ \frac{dI}{dt} = \beta IS - \frac{I}{\lambda} \\ \frac{dR}{dt} = \frac{I}{\lambda} \\ N = S + I + R \end{cases} \tag{3.6}$$

The resolution of this system allows to obtain interpretations, to anticipate the risks that can be caused by the disease, and most important, the resolution of the system helps decision-makers make decisions as soon as possible at the economic or politics situation. We are talking here about dynamic simulation because we study the dynamics of each variable introduced.

Adding these three member-to-member equations, we obtain

$$\frac{dS}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = -\beta SI + \beta SI - \frac{I}{\lambda} + \frac{I}{\lambda} \tag{3.7}$$

Which is consistent with the fact that the population size N is constant, thus of derivative equal to zero:

$$\frac{dS}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = \frac{d(S + I + R)}{dt} = \frac{dN}{dt} = 0 \tag{3.8}$$

The behavior of the variables $I(t)$, $S(t)$ and $R(t)$ of this model can be obtained by simulation, that is to say through the numerical resolution of the associated differential equations. In the simulated model, the variables S and I have been normalized: their value is between 0 and 1 and represent a fraction of the total population. For any simulation, it is necessary to provide:

1. The value of the initial conditions, namely the values of S, I and R at time $t = 0$, i.e. $S(0)$,$I(0)$ and $R(0)$, denoted S_0,I_0 and R_0. In this first scenario, none individual is immunized at first of epidemic period: $R_0 = 0$. And since at any time $I + S + R = N$, it suffices to fix I_0, the initial number of the population of infected people, here a fraction of population N, a value taken between 0 and 1.

2. The values of the parameters, here β and λ.

Before setting values for the initial conditions and parameters, and display the evolution of the variables S, I, R and N, we need to explain the behavior we expect, then we will compare our expectation with the result of the simulation; and we will try to understand any differences. We note that this model is particularly simple, because it carries a lot of very simplifying hypotheses: no mortality linked or not to the disease, uniform mixing of the population, etc., but it's possible to relax some of these assumptions, replacing them with others, less simplifying, and to modify the model therefore. Thus, a term $-\mu I$ permit to take into account the mortality linked to the disease, denoted μ, in the differential equation that governs the evolution of the number of infected persons. So, the equation of I can be noted:

$$\frac{dI}{dt} = \beta IS - \frac{I}{\lambda} - \mu I \tag{3.9}$$

With the addition of this term $-\mu I < 0$, the total population N cannot remain constant. It decreases under the effect of this mortality. The simulation permit to explore the impact of this addition, according to the values of the parameter noted μ. Here again, modify the value of μ, explain the change of behavior that we expect and compare this expectation with the result of the simulation.

The SEI, SEIR, SEIS and SEIRS models

When a susceptible individual is infected by the disease, some time is normally needed before symptoms appear and the individual becomes infectious. One way of taking these effects into account is to introduce a new compartment of exposed individuals E in which all individuals who eventually become infected at a rate k are placed. The system of differential equations becomes:

$$\begin{cases} \frac{dS}{dt} = -iIS \\ \frac{dE}{dt} = iIS - kE \\ \frac{dI}{dt} = kE \\ N = S + E + I \end{cases} \tag{3.10}$$

With these characteristics the compartmental model is called SEI. It's also possible to add such a compartment of exposed individuals to other newly introduced models to obtain models $SEIS$, $SEIR$ or even model $SEIRS$.

3.4.3 Basic reproduction number ($\mathcal{R}_0$)

In an epidemiological study of any disease, one of the first questions the epidemiologist asks is whether there is going to be an epidemic or not. Mathematically, it's possible to answer this question in a simple way by examining the system of differential equations that models the dynamics of the studied disease. Considering a compartmental model, an epidemic implies that the number of patients in compartment I increases, that is to say that there are more new sick persons than new cures. To understand this well, we need to understand the notion of basic rate or number of reproduction or basic reproduction number.

The basic reproduction number, noted $\mathcal{R}_0$, is the number of secondary infections following the introduction of an individual infected in a host population entirely made up of susceptible individuals [Anderson and May, 1992].

$\mathcal{R}_0$ is a threshold that will tell us if there is an epidemic or not:

Table 3.1: $\mathcal{R}_0$ values of some infectious human and animal diseases [Guégan and Choisy, 2008].

Disease	**Host species**	$\mathcal{R}_0$
FIV	Domestics cat	1, 1 - 1.5
Rage	Dog (Kenya)	2.44
PDV	Seals	2 - 3
Tuberculosis	Cattle	2.6
Influenza	human	3 - 4
Foot-and-mouth disease	Ovine	3.5 - 4.5
Variola	Human	3.5 - 6
Varicella	Human	10 - 12
Measles	Human	16 - 18
Whooping cough	Human	16 - 18

- When $\mathcal{R}_0 > 1$ there is an epidemic;
- When $\mathcal{R}_0 < 1$ there is no epidemic, the infection can not settle.

We also note that $\mathcal{R}_0$ permits to compare different diseases. In Tab. 3.1 we present $\mathcal{R}_0$ values of some human and animal infectious diseases.

We note that $\mathcal{R}_0$ is considered as spectral radius of the next generation. This technique was presented in [Van den Driessche and Watmough, 2002]. The determination of the operator involves the division into two compartments; a compartment of infected (latent, infectious, etc.) and a compartment of uninfected individuals (Susceptible and recovered). To illustrate that, we consider an epidemiological model with n homogeneous classes or compartments. The vector x represents the state of the system and x_i is the number (or concentration) of individuals in compartment i. The first k compartments contain all the uninfected individuals or sometimes the opposite. The last compartments contain infected individuals.

The state of the population is note $(x_i), i = 1 \dots n$ with x_i the number of individual in the compartmental i. The dynamic of the model is defined as:

$$\frac{dx_i}{dt} = F_i(x) + V_i^+(x) - V_i^-(x) \tag{3.11}$$

With:

- $F_i(x)$: speed of appearance of the new infected in i, that is to say that which comes from the other compartments and enters i following an infection;
- $V_i^+(x)$: speed of appearance of what goes into i for any cause other than infection;
- $V_i^-(x)$: speed of appearance of what comes out of compartment i.

Let $V_i(x) = V_i^+(x) - V_i^-(x)$ the previous relation of x_i become $x_i = F_i(x) + V_i(x)$

A state x_0 of the system is disease free if the compartments of the "infected" are empty. This is the "Disease Free Equilibrium" (DFE), that is for $i > k, x_0 = 0$ Conditions:

1. $x > 0$ (number of individuals) and by definition the flows $F_i(x), V_i^+(x)$ and $V_i^-(x)$ are positive. If a compartment is empty, then there is no transfer of individuals out of the compartment by death, infection or any other means;

2. if $x_i = 0$ then $V_i^-(x) = 0$ this means that there will not be an exit for an empty compartment;

3. If $i \leq k$ then $F_i(x_0) = 0$ it means by definition that it cannot bring infected people into uninfected compartments;

4. If x_0 is a disease-free state, then $F_i(x_0) = 0$ and for $i < k, V_i + (x_0) = 0$ When there is no infected, there can be no disease, so we remain without infection.

We define the average number of infections produced by an infected individual in a neighborhood of the DFE. Consider the dynamics of the linearized system near the equilibrium point without disease, with a blocked infection:

$\dot{x} = DV(x_0)(x - x_0) = DV^+(x_0)(x - x_0) - DV^-(x_0)(x - x_0)$

the following result specifies the structure of the linearized system $DX(x_0)$ at neighborhood of equilibrium without disease x_0:

Lemma 3.4.1. *If x_0 is a DFE, then the matrices $DF(x_0)$ and $DV(x_0)$ is decomposed as:*

$$DF(x_0) = \begin{pmatrix} 0 & 0 \\ 0 & F \end{pmatrix}$$

$$DV(x_0) = \begin{pmatrix} J_1 & J_2 \\ 0 & V \end{pmatrix}$$

$F \geq 0$ and V is a stable Metzler Matrix.

The detailed proof of Lemma 3.4.1 can be found in [Van den Driessche and Watmough, 2002] . The matrix $-FV^{-1}$ is the second-generation matrix or the next generation matrix.

Definition 3.4.2. ***(Basic reproduction number $\mathcal{R}_0$)***

The basic reproduction number $\mathcal{R}_0$ is the spectral radius of the next generation matrix, as follow:

$\mathcal{R}_0 = \rho(-FV^{-1})$

3.5 Multi-agent systems

As illustrated in Fig. 3.4, a multi-agent system consists of a number of agents interacting with each other. In general, agents will act on behalf of users with different goals and motivations. To interact successfully, agents will have the ability to cooperate, coordinate and negotiate with each other, on a human model [Axelrod, 1997].

3.5.1 Definition

Intelligent Agent

Several authors have defined an intelligent agent. In [Wooldridge and Jennings, 1994] an agent is defined as a computer system located in an environment and capable of autonomous actions in that environment in order to achieve its objectives.

In [Chaib-draa, 1997] an agent is a software that:

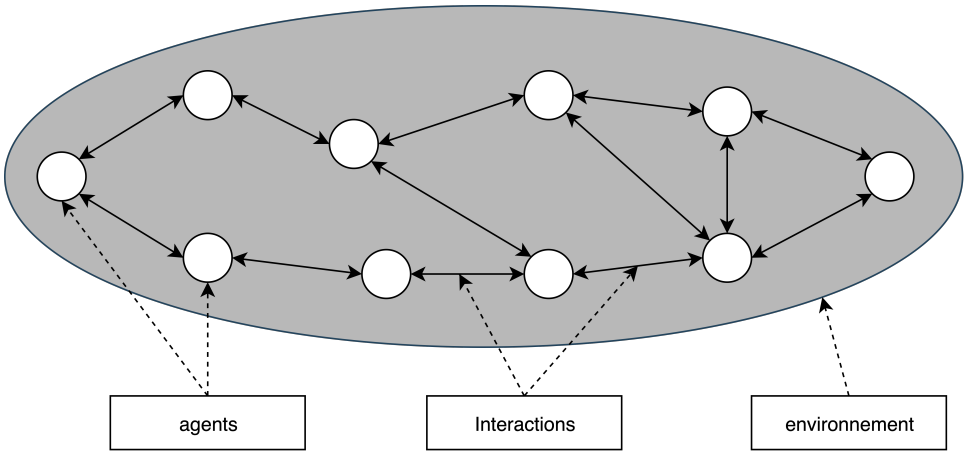


Figure 3.4: Illustration of agents, interactions and environment [Kasereka, 2014]

1. Perceives its environment;
2. Acts autonomously;
3. Interacts to share its goals, its constraints, etc.;
4. Anticipates and reacts flexibly to its environment;
5. Learns from its experiences and adapts to its environment.

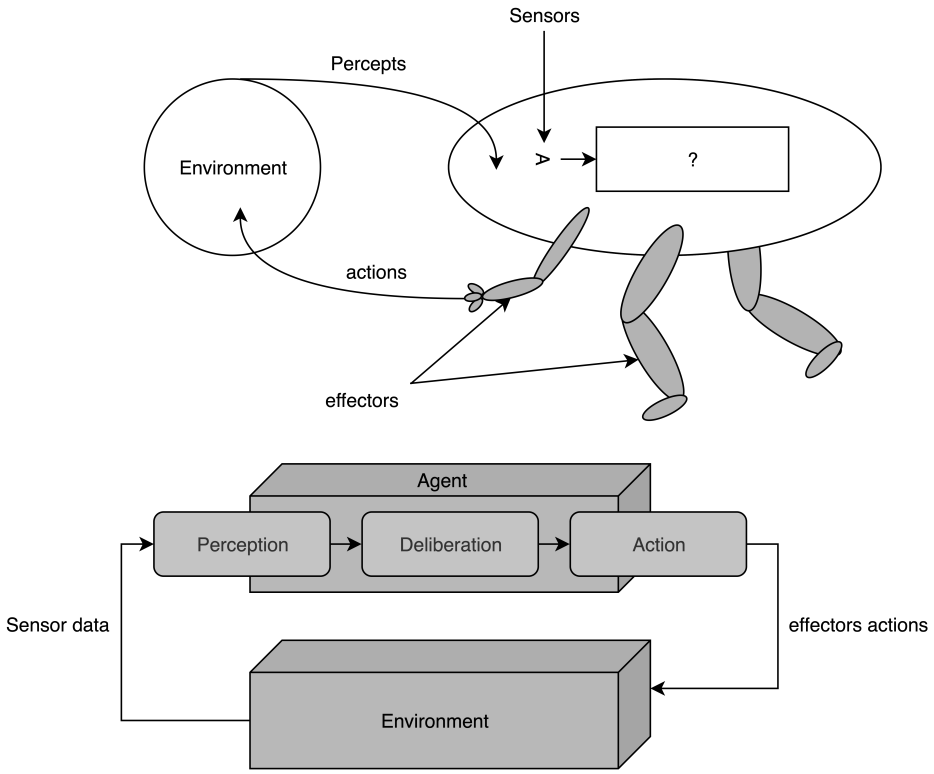


Figure 3.5: Illustration of an intelligent agent acting in an environment [Wooldridge, 2009]

In [Kasereka et al., 2014] an agent is a physical or virtual entity that is able to act in an environment, which can communicate directly with other agents, which is driven by a set of trends (in the form of 'individual goals or a function of satisfaction, even survival, which it seeks to optimize), which has own resources, who is able to perceive (but in a limited way) its environment, which has only a partial representation of this environment (and possibly none), which has skills and offers services. Graphically, an agent can be presented as in Fig. 3.7.

Based on these definitions, we see that an agent is able to interact with other agents on an environment, hence the notion of "multi-agents".

Environment of agents

The representation of environment is an important and difficult task when researchers build a multi-agent modeling-simulation. The environment on which the agents interact may have the following characteristics:

Accessible or inaccessible

In an accessible environment, agent can obtain complete, accurate, real-time information about the state of the environment. The most moderately complex environments (including, for example, the everyday physical world or the Internet) are inaccessible. More accessible an environment is, the easier it is to build agents to operate there.

Deterministic or non-deterministic

In a deterministic environment, each action has only one effect guaranteed (there is no uncertainty as to the state that will result from the execution of an action). But the physical world can be considered non-deterministic. Non-deterministic environments present greater problems for agent designers. The world can be considered as non-deterministic.

Static or dynamic

A static environment remains unchanged unless it is subject to the actions of the agent. A dynamic environment is subject to several independent processes that can modify it. It therefore changes beyond the control of the agent. Other processes may interfere with agent actions (as in competing systems theory). The physical world is a highly dynamic environment.

Discrete or continuous

An environment is called discrete if it has a finite number of elements. Continuous environments are out of step with computer systems (necessarily discrete). The physical world is a continuous environment.

When an environment is simultaneously inaccessible, non-deterministic, dynamic and continuous it said to be open. These types of environments are the most difficult to represent by the Multi-Agent System (MAS).

3.5.2 Agent-Based Modeling (ABM)

Since years, modeling has been applied to many fields and more particularly in the search for the understanding of complex systems. Several modeling approaches used in complex systems are available in the literature [Rey-Coyrehourcq, 2015]. Fig. 3.6, summarized in [Drogoul and Gaudou, 2013], illustrates the main approaches for modeling the dynamics of complex systems. Most analytical approaches are based on mathematical equations and therefore give the evolution of the system at the macroscopic level (population level for example). On the other hand, generative approaches model the system at the individual level (microscopic level). Agent-based modeling is the most recent approach, it is applied in most life sciences such as economics, geography, ecology, etc. [Gaudou, 2016].

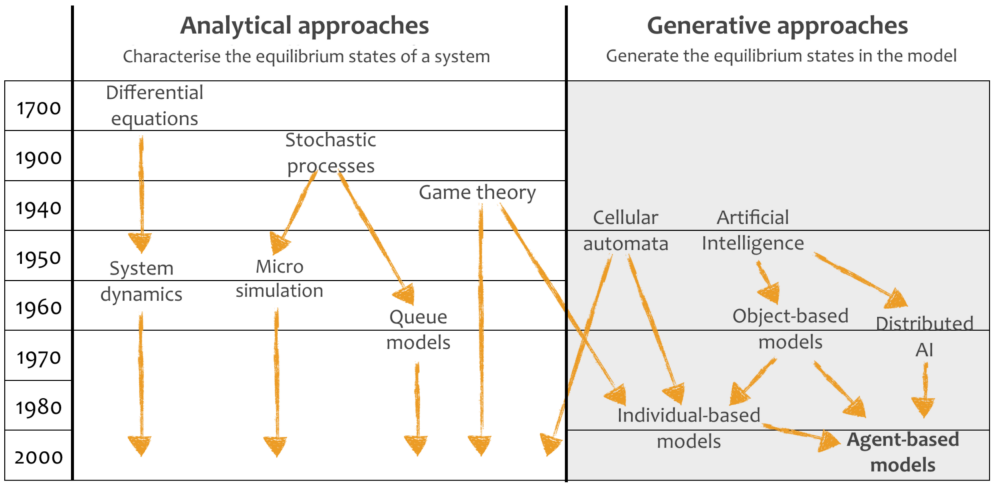


Figure 3.6: Modeling approaches over times in Social Science [Gaudou, 2016]

ABM is based on intelligent agents. These models are both stochastic and individual. These approaches are interesting because the behavior of each agent is described by an algorithm, they are most realistic. The system is more accurate because it is possible to consider an individual level and considering of a geographical representation of interacted entity.

Nowadays, biologists, mathematicians and computer scientists collaborate to develop tools to simulate spread model of infectious diseases to test the foundation of these models. A first approach in modeling - simulation of population dynamics, spread of disease, etc. is based on solving differential equation system corresponding to the studied model. A second approach consists of individual-centered modeling-simulations, namely the study of interactions between different individuals and with their environment.

Properties of ABMs

Based on the hypothesis of compartmental models we find that they don't have power of representation to be able to examine a heterogeneous population. Therefore, new paradigms of representation or meta-models are needed: micro-simulation can represent the heterogeneous population and any cellular automata can take into account the (spatial) structure of the population. But these approaches have certain limitations that can be addressed by the use of agent-based models [Quesnel, 2006].

Agents may represent individuals, households, governments or any other entity of interest. These agents can adapt their behaviour according to interactions with other agents and interactions with their

environment and individual experiences. An important feature of agent-based modeling is that, based solely on all individual behaviours, it allows the emergence of phenomena at the population level or different from those expected [Tracy et al., 2018]. It is a bottom-up approach, in which behaviours at the microscopic level generate dynamics at the macroscopic level [Epstein, 2009].

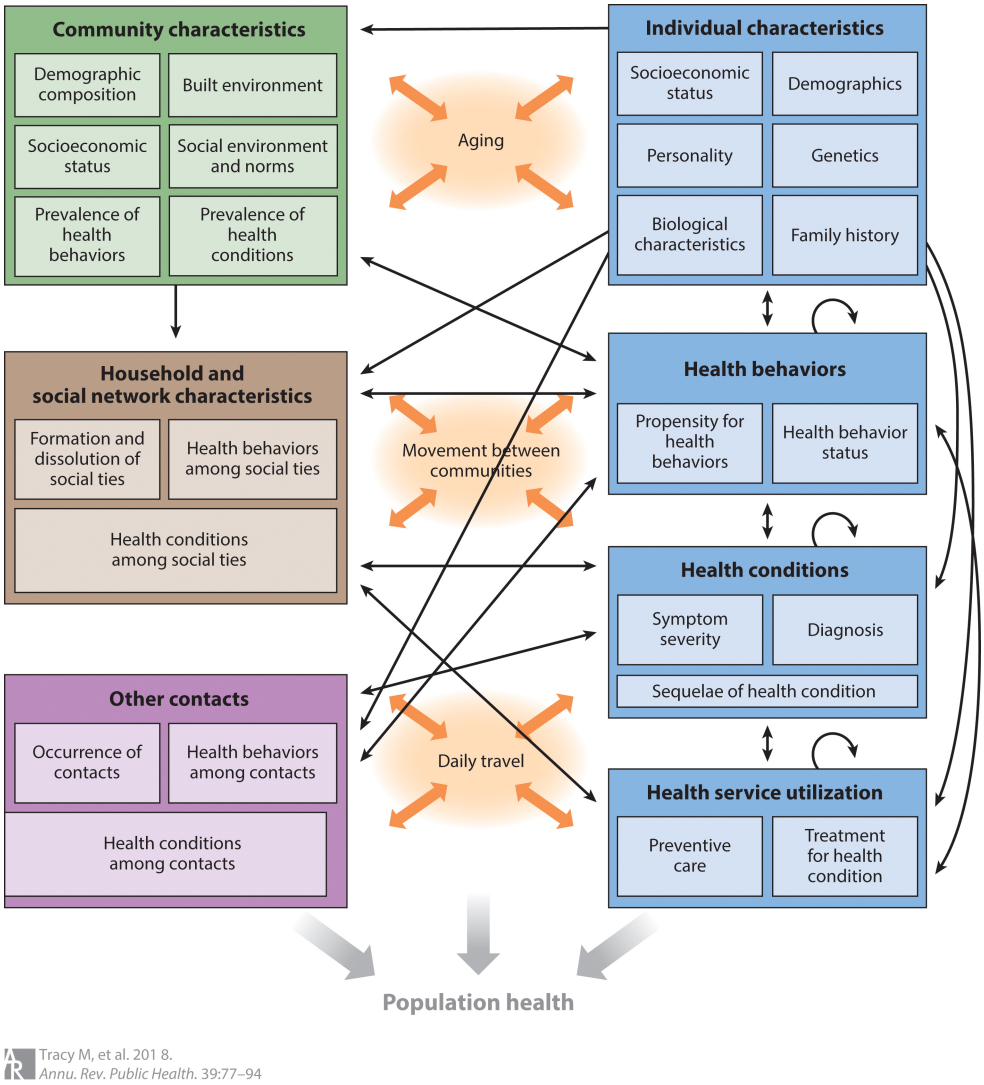


Figure 3.7: Properties of ABMs [Tracy et al., 2018]

Other properties of agent-based modeling include stochasticity, autonomy, feedback and heterogeneity. Stochasticity adds randomness to the problem solving, in other words it allows the model to proceed in a probabilistic (as opposed to deterministic) manner, so chance influences the model's behaviors. Autonomy implies that agents decide how they should act according to their current situation and the programmed rules of behaviour [Tracy et al., 2018]. Feedback refers to the feedback from a system when a parameter is changed. It can be positive or negative. Heterogeneity can be seen in the differences between agents and between parts of the environment, which can have multiple static and time-varying characteristics. These variations can be unexpectedly amplified over time through feedback, past experiences that can change future responses [Tracy et al., 2018].

Thanks to these properties, agent-based modeling can be applied to take into account non-linear

relationships influenced by multiple levels and interpersonal interactions in a way that is often more flexible than that offered by other approaches. This approach therefore makes it possible to address many research questions that other traditional analytical approaches cannot solve, such as the mathematical approach based on ordinary differential equations.

It is known that mathematical models are well suited to modeling high-level system behaviour in large populations [Lofgren, 2017, Luke and Stamatakis, 2012]. These models do not accurately specify the behaviours of individuals at the microscopic level, including interactions between these individuals and adaptations over time. Agent-based models complement and extend other approaches by integrating network dynamics, while taking into account multi-scale interactions and bidirectional feedback loops between model entities. These models were developed as a result of advances in computer science, mathematics, physics, game theory and others during the 2nd century in the field of information processing, including genetic algorithms and automata [Luke and Stamatakis, 2012].

ABM in Public Health

In public health, agent-based modeling has been used almost exclusively in the past to model the transmission and control of infectious diseases in populations [Tracy et al., 2018]. Considering the characteristics and benefits listed in the previous section, agent-based models are a natural and better choice for modeling the dynamics of infectious diseases in the population, as taking into account interactions between individuals and also with their environment often results in population models that are as close to reality as possible. As a result, agent-based models have gained ground. Currently they are applied in understanding the dynamics of non-communicable diseases, health behaviours, social epidemiology and other issues relevant to population health that do not involve traditional infectious processes [Nianogo and Arah, 2015]. They are therefore full-fledged tools for realistic simulations of a well-defined population [Tracy et al., 2018].

For infectious diseases, agent-based models are generally based on the SIR model proposed by Kermack and McKendrick. These SIR-based agent models have been used to introduce individual heterogeneity and interactions into more complex networks in these aggregated compartmental models. This has led to a better understanding of the dynamics of infectious diseases in real environments [Epstein, 2009, Chowell et al., 2016].

Limitations of agent-based models

It is true that agent-based models have many advantages, but it should be noted that some important limitations and challenges related to the nature of the development and configuration of agent-based models exist. These limitations and challenges must therefore be taken into account when interpreting the results of the model implemented.

One of the main challenges in designing and implementing an agent-based model is the palpable tension between simplicity and realism of the model [Tracy et al., 2018]. Here, finding a balance between the desire to make a simplified representation of reality and the need to include enough complex elements to provide new ideas becomes difficult to master [Kalton et al., 2016]. To build size models, we need to adopt an approach that gradually adds complexity when justified and works with various stakeholders to identify the essential and necessary elements for understanding the system [Auchincloss and Garcia, 2015, Roux, 2015].

Another challenge remains the uncertainties related to the resolution of models due to the parameterization of models in the absence of empirical data. In addition, there is the validation problem, which is difficult when empirical data are scarce, because ideally, the data used for model validation should be independent of those used to construct and calibrate the model.

It should be noted that the lack of training in agent-based modeling techniques for students, researchers and public health professionals, the considerable time and computer resources required to develop, execute and validate these models can constitute a logistical barrier to their successful development [Tracy et al., 2018].

3.5.3 Model description with ODD (Overview, Design concepts, Details) protocol

ODD was introduced in [Grimm et al., 2006] with the aim of making the model easier to read and write and also to facilitate replication. This formalism is independent of discipline, complexity, operating systems and even programming language. It is therefore a standard formalism that allows the description of individual-centered and agent-based models. It has been updated in [Grimm et al., 2010]. This protocol is presented as follows:

Overview

- Purpose: here, we have to show the purpose of the model;
- Entities, state variables, and scales: we have to show the types of entities that are included in the model set up. For this we must define the state variables and the behavioral attributes. We must also show the temporal and spatial ranges of the implemented model;
- Process overview and scheduling: here it must be said which entity does what and in what order. It is also necessary to show in which case the state variables are updated and to specify how time is modeled (discrete or continuous).

Design concepts

- Emergence: show what emerges from the model;
- Adaptation: specifies how the agents adapt to improve their physical form in a direct and indirect way;
- Fitness: shows the agents' objectives and specify what determines their survival;
- Prediction: shows how agents predict the consequences of their decisions. For this it is necessary to use learning, memory, environmental indices and / or integrated hypotheses;
- Detection: defines the agents' perception. This will show what the agent perceives when he makes a decision;
- Interaction: sets up all forms of interaction between practicing agents;
- Stochasticity: justifies any stochasticity existing in the model implemented;

- Collectives: shows if there are groups of individuals;
- Observation: shows how the data is collected from the model for analysis.

Details

- Initialization: defines the initial state of the model environment. We must define the state of the system at time t = 0;
- Input data: say if the model uses data from external sources;
- Sub-model: shows the sub-models which represent the processes presented in the point "Process overview and scheduling". Defines all the parameters of the model, their dimensions and their reference values.

3.5.4 Recommendations of agent-based modeling

This agent-based approach is set to progress, which will make it possible to try, to some extent, to meet some of the challenges of these models. A recent paper [Tracy et al., 2018] encourages modellers to include several types of risk factors in models in order to identify the links between scales; this may include genetics, biology, behaviour, environment and contact networks.

Coupling these models with other models from other approaches would make it possible to capture the emergence of modelled systems at different scales and thus understand their evolution over time through bottom-up modeling.

3.6 Equation-Based Modeling (EBM) vs. Agent-Based Modeling (ABM)

Essential advantage of modeling using equations (Equation-Based Modeling) is that this approach is formalized. A mathematical equation is universally understandable, analytical solutions can be found and if not, numerical simulations can be performed. A system of differential equations can describe the evolution of a population of cells or many types of interactions between several cell populations. But it should be noted that this formalism is however confronted with several types of problems [Kasereka, 2014]:

1. The calculation performed is the average behavior of the system, the case where the number of certain molecules is low is therefore poorly taken into account by this type of modeling;
2. Networks with real size, with a hundred interactions are difficult to model by a set of differential equations;
3. Introduction of new populations into the system and improvement of the model require modification of most equations of the model.
4. Differential equation modeling requires a high level of abstraction.

Modeling by equation	Modeling by Agents
Synthetic	Many parameters
Mathematical resolution	Calculation is more needed
Formalized	Not formalized
Not close to biology, abstract	Close to biology
Little modular and little incremental	Modular and incremental
Description in a population level	Description in an entity level (cellular, molecular, etc.)

Table 3.2: Comparison of Equation-Based Modeling and Agent-Based Modeling [Kasereka, 2014]

The main advantages of multi-agent modeling lie in its modularity and incrementality. Modularity allows easy addition or removal of one or more agents. Incrementality means that the theorist can easily improve, refine the agents that make up its system.

In a multi-agent approach, the behavior of each agent is described by an algorithm. Therefore, the system is more accurate and detailed than a global description that includes an entire population.

In addition, the modeling of multi-agent systems is more realistic than the differential equation approach. Indeed, there is a great analogy between multi-agent modeling and the systems of cellular biology. In other words, the level of abstraction is low when the multi-agent modeling is used. Unfortunately, this approach has some disadvantages. It is impossible to obtain an analytical model from an agent simulation [Kasereka, 2014]. The description of the system implies a consequent increase in the number of parameters with respect to an equation description. Finally, the agent simulation requires a high computing power. The Tab. 3.2 gives a summary of the advantages and disadvantages of EBM and ABM.

Based on the elements provided below, we see that these two approaches can easily complement each other.

3.7 Computer simulation

Researchers have several strategies when they want to work on a particular phenomenon. They can collect data on this phenomenon and study them using statistical tools, they can conduct real experiments in the laboratory, and finally they can try to recreate the phenomenon using a computer simulation.

In [Drogoul, 1993] computer simulation is defined as a scientific process that consists in creating an artificial reproduction called a model of a real phenomenon that we wish to study. Computer simulation is used when the analytical approach proposed by statistical or mathematical models is insufficient, when we wish to imitate the mechanisms of a real process that are difficult to reproduce experimentally or to put in equation form or when we wish to elaborate a theory and we don't have enough solid knowledge about it.

Simulation is also defined as the process of designing a model of a real system and conducting experiments on the basis of that model to understand the behavior of the system or evaluate different strategies for its operation [Shannon, 1977].

The objective of the simulation is to facilitate the understanding of the dynamics of a system and to try to predict its evolution. Satisfying of this objective requires the development of a model of the system to be studied, its execution on a calculator / computer, and the analysis of the results of this execution [Fishwick, 1997].

The simulation model generally refers to the set of mechanisms that manage system state changes. It corresponds to the set of laws, conditions or constraints that define the behavior of the system, as well

as the way in which its components are aggregated. The execution process must evolve over time the model of the system [Coquillard et al., 1997]. To achieve this, it usually associated with a set of tools who constitutes the simulator. Three main families of simulation models can be distinguished, we mention the macroscopic, microscopic and mesoscopic models [Karafyllidis and Thanailakis, 1997].

3.7.1 Macroscopic simulation models

This type of simulation focuses primarily on regions or populations rather than on individual behaviors. These models were originally developed to model transport traffic, such as highways, street networks, and rural roads. This approach allows the simulation of a very large population with a relatively low cost of calculation. However, because of its high level of representation, the results are aggregated, inaccurate and related to the size of the simulated population.

3.7.2 Microscopic simulation models

These models focus on the movements of people based on dynamic and individual behaviors. These models are effective for evaluate congestion and saturation conditions of a system, studying the topological configuration of the system, and evaluating the impacts of individual behaviors on that system. However, these models are difficult to implement, expensive in terms of computing time, and can be difficult to calibrate.

3.7.3 Mesoscopic simulation models

These models combine the properties of microscopic and macroscopic simulation models. For example, they can focus on entities who compose the system using models that do not distinguish individuals from each other such as particle models; by grouping individuals into higher level entities such as groups of pedestrians, or by using a discrete model of the environment such as cellular automata.

3.8 Some models for controlling and understanding the spread of tuberculosis in the population

3.8.1 Modeling tuberculosis dynamics with the presence of hyper-susceptible individuals for Ho Chi Minh City from 1996 to 2015 [Vinh et al., 2018]

Context of the study

In this paper the authors propose a mathematical model to study the dynamics of TB in Ho Chi Minh, a city in Vietnam considered to be the one that bears the burden of TB in that country. There are also many cases of HIV in this city and this creates a large number of people who are hyper-susceptible to tuberculosis. This study was based on the dynamics of the disease in this particular population by considering endogenous and exogenous infections.

Methods used

The model used in this study is based on the one applied in [Rodrigues et al., 2007] with some modifications. In this model authors consider 2 groups named G1 and G2. The first, G1, describes the dynamics of

people who are not hyper-susceptible and the second, G2, describes the dynamics of hyper-susceptible people. And these are two major compartmental models because there are links between the two groups. Based on the description presented here, the authors construct a deterministic model by presenting it as a system of ordinary differential equations. From this system, the force of infection or incidence is obtained. Simulations were performed on the proposed model using Ho Chi Minh City data from 1996 to 2015. The maximum likelihood method used to estimate the model parameters. The authors simulated 4 scenarios based on contact parameters and the relapse rate of people with TB over 20 years. The Akaike criterion is applied to compare the fixed scenarios and find the most likely one based on the data and the TB situation in the city.

Overview of the obtained results

The results obtained by the authors show that the 4^{th} scenario, which considers that contact parameters and relapse ratio vary with time, is the most likely compared to others based on data from 1996 to 2015. The implemented model showed how HIV drives TB dynamics in HCM city. This work suggest that for hypersensitive individuals, the reason for reducing the risk of relapse of active tuberculosis is the delay in the treatment of HIV.

Criticism

The model implemented here is interesting in the sense that it considers people with susceptible tuberculosis and those with hypersensitive tuberculosis. The use of real data from Vietnam, precisely the Ho Chi Minh city, is one of the strengths of the model proposed by the authors. But, we note that the model consider only one city. Thus, the contribution of individuals entering/exiting the city on the epidemiology of the city is not highlighted to calculate the strength of the infection. Taking into account the movements of individuals should, in a certain way, make it possible to have an idea of the impact of the mobility of individuals on the force of infection (incidence).

3.8.2 An agent-based simulation of TB epidemic: Understanding the timing of transmission [Kasaie et al., 2013]

Context of the study

The authors are based on the fact that the transmission of diseases that spread through the air has been incomprehensible for decades. However, it is essential to understand how a disease spreads in order to try to eradicate it. TB is one of these diseases whose transmission process remains difficult to understand. For example, it is difficult to differentiate a primary infection from a progression to active TB, re-infection, and reactivation of a latent person. It should also be noted that it is difficult to have data from a transmission chain on a contact network in a retrospective study and also cohorts are very expensive. If the transmission of a disease is understood, it makes it possible to design and implement it, but also to strengthen the control of interventions and reduce the transmission rate.

Despite extensive studies in modeling and simulating the spread of TB in a population, the relationship between disease duration, symptom burden, contact network, diagnosis/treatment and contamination remains abstract and incomprehensible. In order to fully understand this transmission, the authors

proposed to set up a simulation based on agents in a population located in a city. They therefore studied the dynamics of TB transmission and the role of various contact networks in the spread of TB.

Methods used

The authors consider that agents represent individuals. These individuals have their own characteristics, social relationships, and status (+/-) with respect to TB. In this research, it was considered that the epidemic exists. A 3-level hierarchical structure (generally used for airborne diseases) is the one considered in this work, we quote household members, neighbourhood residents and community members as illustrated in Fig. 3.8 below.

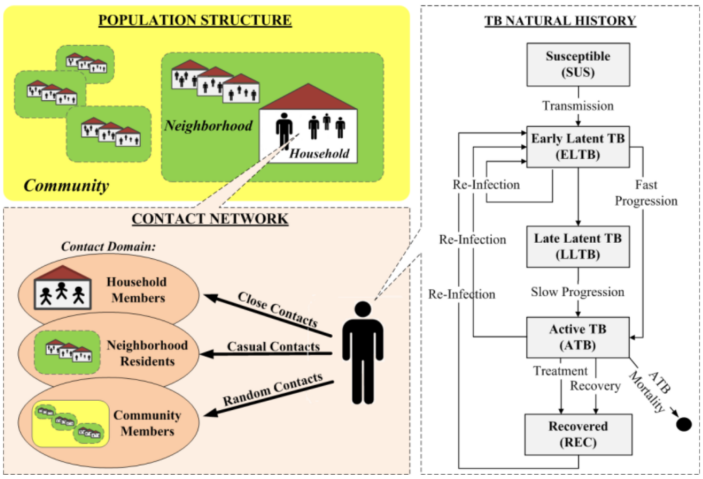


Figure 3.8: Schematic illustration of the proposed agent-based model, population structure and contact networks. [Kasaie et al., 2013]

Researchers model TB transmission at the individual level and also the time required to have a secondary infection from a single source during the course of the disease. Based on the above-mentioned 3-level population structure, they define a three-layer contact network. We have close contact (members of the household), occasional contact (residents of the neighbourhood) and random contact (members of the community). The following parameters were used for the different contact networks: domain (average population size), disease duration, target network size, probability of attendance, estimated network size for a long-term individual, contact effectiveness. We should note that the simulation was conducted on a community of 2000 households in 50 neighbourhoods. The model proposed by the authors is calibrated to a high incidence (120 per 100,000 persons/year). The probability of procreation is adjusted so that the population remains constant. For this model, the authors chose a transitional simulation period (100 years) such that the external infection rate (reinfection of latent persons) is less than 5% and the incidence rate has a stationary mean. The analysis of the results begins in year 101.

Overview of results and discussions

The results obtained by the authors show that the average frequency of infections in a single individual with tuberculosis changes throughout the contagion. In Fig. 3.9, we can see the number of secondary infections stratified according to the type of contact. In this figure, all three curves have a similar general

pattern. These results show that this number of infections increases in the first few months as infectivity increases, then decreases as the infectivity period ends.

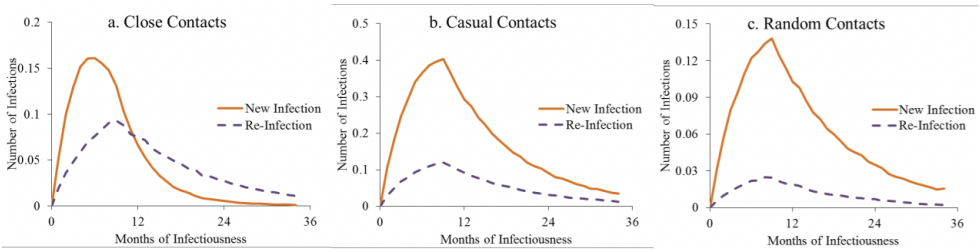


Figure 3.9: Number of secondary infections stratified by type of infection. [Kasaie et al., 2013]

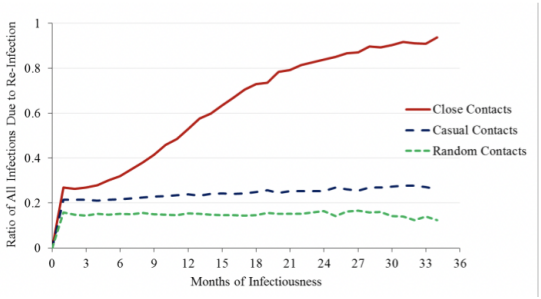


Figure 3.10: Ratio of all infections representing re-infection. [Kasaie et al., 2013]

Fig. 3.10 shows that there are more reinfections in the close contact network, followed by the occasional contact network and finally the random contact network.

Criticism

This model is interesting in the sense that it takes into account a 3-level population structure associated with a specific contact network. One of the strengths of this work is that the authors carry out a comparative study of transmission models between different contact networks and also carry out a sensitivity analysis of the output results of the simulations.

But we note that this work does not use real data and therefore remains not validated. Also, the authors do not clearly specify how a specific individual can be found in different networks at given times. For example, the model could define an individual's travel time from a source to a chosen destination and specify his or her membership in a specific network for any t time. This can help to understand the effect of mobility on the evolution of TB incidence in different contact networks.

3.8.3 An agent-based computational model of the spread of TB [De Espíndola et al., 2011]

Context of the study

This paper is based on the mathematical model of TB proposed by Blower et al. [Blower and Gerberding, 1998] [Blower et al., 1995] [Blower et al., 1998]. The authors develop a model based on agents of TB spread but also the emergence of drug resistance due to antibiotic treatment. In this work, the idea was therefore

to give the possibility to explicitly represent heterogeneity at an individual level and to visualize the model of TB spread in the population at any time during the evolution of the system.

Methods used

In this paper, the authors consider the spatial structure of the population. To do this, they construct a model in which individuals (agents) are placed on a square shaped environment of size $N = L \times L$. In this sense they define $I_{i,j}$ as an individual placed on this environment with $i, j \in \{1, 2, \ldots, L\}$. An individual $I_{i,j}$ can be in one of the following states: Susceptible X, Latent (L_S for sensitive and L_R for resistant) or Infectious (T_S for sensitive and T_R for resistant) as shown in Fig. 3.11 below. All transitions between sub-funds are defined in terms of probability. In this model, healed or dead individuals are replaced by susceptible individuals, this replacement is done to reproduce the recruitment rate used in the differential equation model on which the authors rely. This mathematical model can be found in [Kasaie et al., 2013].

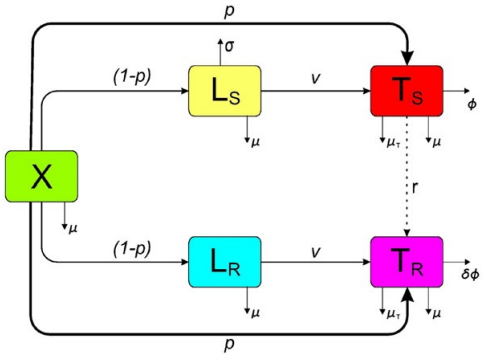


Figure 3.11: Schematic representation of the interaction between the five states of TB [De Espíndola et al., 2011]

.

Two origins or sources of contamination are considered in this model. The local level, when a susceptible individual is in close contact (neighbour) with an individual T_S or T_R and the global level is when the susceptible individual is in contact with the rest of the network members. To do this, the authors define a probability of contracting the disease. For a local infection, this probability is defined as follows:

$$P_{LK} = 1 - (1 - \beta_K) \tag{3.12}$$

With β the probability of being infected and $K = \{S, R\}$

Hence the total probability of having a local infection susceptible to S or resistant R is given by:

$$P_{Lt} = P_{LS} + P_{LR} - P_{LS}P_{LR} \tag{3.13}$$

The probability that an individual will be exposed to a global infection (contaminated by another person in the network) is defined by:

$$P_{GK} = \beta_K \frac{T_{TK}}{N} \tag{3.14}$$

With $K = \{S, R\}$ and T_{TK} the total number of infectious individuals without treatment.

And the total probability of having a global infection susceptible to S or resistant R is given by :

$$P_{Gt} = P_G S + P_{GR} - P_{GS} P_G P_G R \tag{3.15}$$

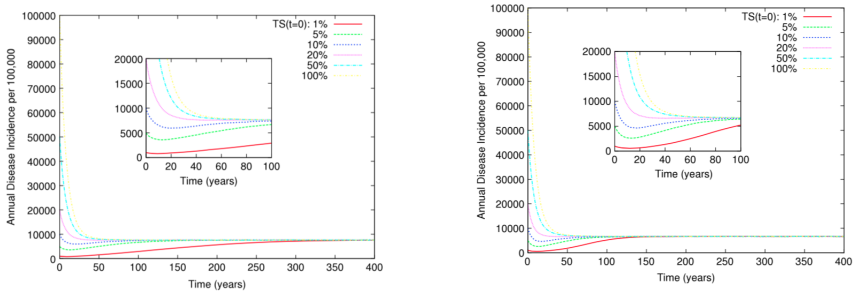
It should be noted that if there is co-infection with the two pathogens S and R, the individual is considered to be infected with the pathogen R. In this model, a random number of latent individuals are subjected to chemoprophylaxis (affecting only L_S individuals). During this treatment, these individuals may become susceptible (X) or infectious (T_K) according to a probability or either remain latent. Those who have not received treatment remain latent or progress to infection (T_K).

For infectious individuals (T_S and T_R), a random number is taken to follow antibiotic treatment. Three situations are possible for this proportion of individuals: either the treatment is successful and therefore the infection is cleared, or the individuals develop antibiotic resistance due to the failed treatment, or the individuals finish the treatment without healing but also without developing antibiotic resistance and remain in T_S.

At the beginning of the simulation of this model, at $t = 0$, the authors consider only the presence of individuals X and T_S (20% of the total population with a random and uniform distribution), and consider that there is no intervention from a health program (no TB treatment) until the time $t = 199$ which represents 199 years. At the end of this period on the environment we have the individuals X, L_S and T_S. It is therefore from the first day of the 200th year that chemoprophylaxis and antibiotic treatment begins for a proportion of people randomly selected from the L_S and T_S individuals.

Overview of Results and Discussions

Interesting results have been obtained by the authors. They use several scenarios to see the evolution of TB in the population. For example, the model tests the different TB treatment regimes and also the impact of the type of contamination (local or global). In Figs. 3.12a and 3.12b we can see the incidence of TB in a network model representing 400 years for different initial proportions of infectious individuals T_S when we do not take into account the intervention of the health system. In Fig. 3.13, the intervention of the health system through the treatment and administration of chemoprophylaxis to subjects L_K starting on the first day of the 200th year is considered.



(a) (b)

Figure 3.12: TB evolution in the model over 400 years with a zoom from 0 to 100 years. (a) when only local interactions between individuals are considered and (b) when only global interactions between individuals are considered. [De Espíndola et al., 2011]

Several other results have been obtained in this research, including the one that shows that if 38% of individuals T_S receive chemoprophylaxis, the S bacteria type will disappear from the population. This is

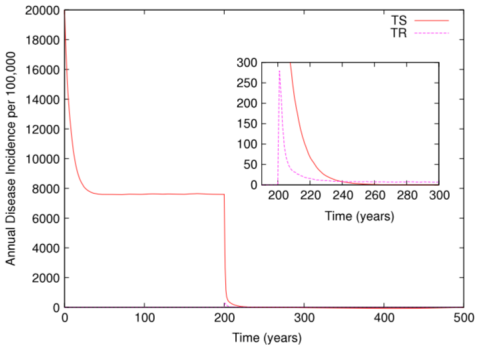


Figure 3.13: TB evolution in the 500-year model with a zoom of the period from 190 to 300 years. Processing is taken into account from the 200th year onwards. [De Espíndola et al., 2011]

therefore interpreted as a strong suggestion to public health policies that should pay more attention to tuberculosis prevention as soon as a person is detected with the virus. It should be noted that the model proposed by the authors was validated by reproducing the results already known in the literature.

Criticism

The work done by the authors in this research is interesting in the sense that several scenarios are considered. The fact that the model takes into account the spatial structure of the population makes it possible to carry out good experiments.

But we note that, in this model, the population structure is not well known. For example, the concepts of local and global contamination are not well defined. The model does not clearly show where the so-called local network in which local contamination occurs is limited. In addition, this model does not use real data and the location of populations on the environment remains uncertain. Taking into account the GIS should make it possible to highlight several other interesting results, particularly those related to population mobility, especially since this model simulates the evolution of TB over several years.

3.8.4 Timing of Tuberculosis Transmission and the Impact of Household Contact Tracing. An Agent-based Simulation Model [Kasaie et al., 2014]

Context of the study

In this paper the authors base themselves on the fact that in the literature the transmission time of TB and the relationship with follow-up of household contacts is not very clear. To do this, they seek to increase the impact of contact tracing in households within a population. This involves identifying and treating household members who have been diagnosed with active tuberculosis (ATB). To achieve this, the authors implemented an agent-based model. The same authors had already presented in [Kasaie et al., 2013] the global model on which they are based. In this work, the authors wanted to show that household contact tracing can reduce the incidence of TB in the studied population and that this could persist for many years after health policy intervention has stopped.

Methods used

In this research, the authors use a transmission model applied in [Kasaie et al., 2013], but for the population structure they consider that the population is structured as households and communities. Therefore, the contact network to consider is close contact (in households) and occasional contact (in the community). This information is illustrated in Fig. 3.14 below.

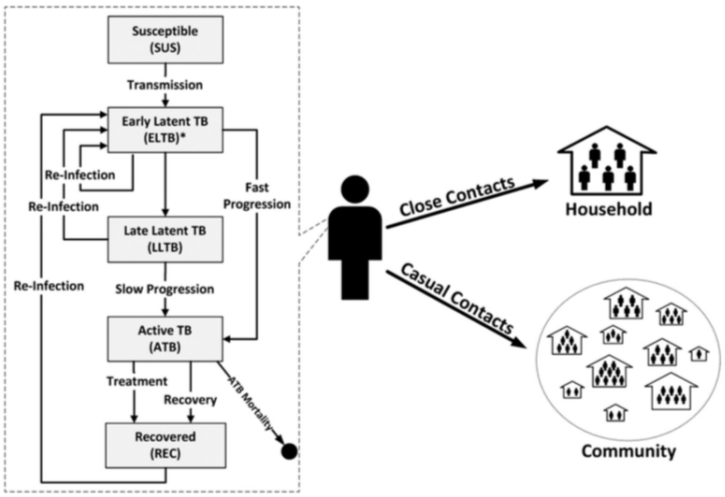


Figure 3.14: Illustration of the proposed model, population structure and contact networks. [Kasaie et al., 2014]

As in [Kasaie et al., 2013], the authors considered 2000 households ranging in size from 1 to 10, and as a discrete triangular distribution of 5 people. In this model, individuals are characterized by household membership and TB status (+/-). Two sources of contamination/transmission are considered, the first is household members (close contact) and the second is the community (occasional contact). Each type of contact is associated with a frequency and efficiency parameter that determines the probability of TB transmission in each network. In these networks, the authors assumed that an individual in the household must contact all household members and some community members. The time step chosen was 1 month. We also note that the risk of transmission by contact is calibrated so that the model gives an incidence of 120 per 100,000 person/year.

Since the proportion of transmission is not the same between household and community, the authors constructed two scenarios based on the data. This is where the authors insert the HHCT (Household Contact Tracer) mechanism. To do this, a proportion of passively diagnosed individuals are selected and treated for active TB. To estimate the impact of HHCT, the authors considered 100% sensitivity to diagnose active TB individuals but also the level of coverage of the low population.

Overview of results and discussions

A number of experiments have been carried out in this work. The results obtained show that by calibrating the treatment time of individuals to an average of 11 months, individuals infected by casual contacts were infected by individuals who have been infectious for more than 11 months. In contrast, if low active TB infectivity is considered during the first 9 months, the majority of new infections among household members occur within 4 months for household-based scenarios (95% new infections) and 7 months for

community-based scenarios (75% new infections). And also the infection rate in households reaches its peak 3 to 5 months rather than that of community contacts.

The results also show that if 100% of individuals were identified, tested and treated, the incidence of TB could decrease by 10% (from 120 per 100,000 persons/year to 108 per 100,000 persons/year) after 5 years. And if the intervention is stopped after 5 years, the incidence will continue to fall for 2 years and remain intact 15 years after the intervention is stopped in both types of contact networks as shown in Fig. 3.15 below.

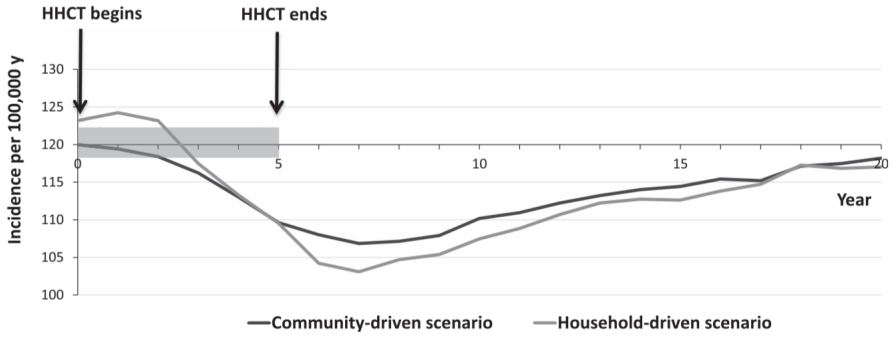


Figure 3.15: Illustration of the evolution of the incidence during the intervention (5 years) and after the end of the intervention. [Kasaie et al., 2014]

These results provide information on the role of household structure in TB transmission in the population and can easily help authorities to better project the epidemiological impact of HHCT interventions on TB in the medium term. The results also support that the combination of HHCT with PT (Preventive Treatment) may significantly reduce TB in the population.

Criticism

In this work, it was demonstrated that tracking or contact tracing in a target population could significantly reduce the rate of TB contamination in different contact networks considered.

But we note that this model suffers from the same shortcomings as [Kasaie et al., 2013]. Indeed, it is difficult to understand how and when (for example, during the day) people move between different networks.

3.9 Conclusion and positioning

In the literature, only limited work has been done on agent-based modeling of TB spread in the population. Yet, this way of modeling and simulating disease dynamics makes it easy to explore many factors that are difficult to apply in mathematical modeling.

With the work presented here, it is clear to see that we have, with ease, the possibility of taking into account the spatial structure of the population and associating several types of contact networks with it when we do agent-based simulation. This modeling/simulation allows the possibility of explicitly representing heterogeneity at the individual level and also allows the visualization of the disease spread model at any time during the evolution of the system.

But we note that the coupling of these models presented in this document to the GIS (Geographic Information System) could explore many other aspects that may allow a more in-depth understanding of TB dynamics in the population. Using the Geographic Information System for a specific region, we can easily examine, for example, the correlation between transport (road/air) and TB infection in a population. We can also, for example, study the impact of physical contact and individual mobility on TB dynamics in a population based on the GIS.

We also note that during our research, we did not find any work coupling models from these types of modeling (ABM) with mathematical models from differential equation-based modeling (EBM) for the spread of TB in the population.

In this chapter, we presented all information necessary about modeling and simulation of infectious disease. Two kinds of modeling the same situation was presented, Agent-Based modeling and Equation-Based modeling. We tried to compare these two kinds of modeling by showing advantages and disadvantages of each other. We conclude that the two modeling can be complementary and can be used simultaneously without problem. Some works on modeling and simulation of TB using ABM and EBM was also presented. Through this study, we were able to see how the other authors modelled and simulated TB in the population. These study allow us to have a own position.

In the next chapter, two mathematical models are proposed, their analysis and simulation are presented. Discussions of results are also presented.

Chapter 4

Mathematical modeling and simulation of pulmonary tuberculosis, case studies of Democratic Republic of the Congo

In this chapter, we propose two mathematical models (named MODEL 1 and MODEL 2), their analysis is also described. Indeed, the models are based on the natural history of TB transmission, discussion with experts in the field about taking care of TB infection in DRC, but also are based on data at our disposal. Parameter values are found from the literature and based on data.

4.1 MODEL 1: Analysis and simulation of a mathematical model of pulmonary tuberculosis in the population

4.1.1 Introduction

The study of the infectious diseases dynamics is one of the most important and essential tasks to be done in order to have a good understanding of the emergence of diseases in a population. If until now, there are diseases that continue to ravage populations in low- and middle-income countries, such as the Democratic Republic of the Congo (DRC), it is largely due to the lack of understanding of the dynamics of these diseases. Despite government efforts and extensive research to control TB transmission in Congo, the disease continues to spread and settle in various parts of the country. The study of the spread of diseases allows decision-makers to try to eradicate them in the population based, for example, on the results of simulations or any other experiments. It can also help to make predictions and thus to make a good decision at the right time.

In order to identify ways to control diseases in the population, several studies have been conducted in mathematics [Goufo et al., 2016, Goufo et al., 2017, Atangana et al., 2014, Djomegni et al., 2017]. Mathematical models are developed and applied in ecology, and also are used to understand epidemiological phenomena [Kasereka et al., 2014, Kasereka et al., 2018b, Leon et al., 2017]. One of the main objectives of these mathematical models is to try to understand how a given disease spreads in the population, in order

to try to eradicate it in the future [Ndondo Mboma, 2017, Ndondo et al., 2016]. In other words, mathematical models attempt to answer the question of how to control a disease (prevention and surveillance) in the population.

Several mathematical models of tuberculosis have been developed. These models have a significant role to play in the process of controlling TB worldwide that is ongoing. In the literature, these mathematical models are compartment one. Compartmental models are used since years. The Kermack and Mac Kendrick model is one of those models on which current models are based [Goufo et al., 2014]. Most of TB models we find in the literature are of the SIR [Iskandar et al., 2017] or SEIR type [Blower et al., 1996a, Castillo-Chavez and Feng, 1997, Feng and Castillo-Chavez, 1998, Feng et al., 2001, McCluskey, 2008, Murphy et al., 2002]. Basically, there are groups or class of individuals, each group has a status that characterize it as susceptible (S), latent (E), infectious (I) or recovered (R). The transition of individuals from one group to another is generally defined by a proportion and/or a rate.

In this work, we model, analyze and simulate a mathematical model of the dynamics of pulmonary tuberculosis with eight compartments that include groups of individuals lost to follow-up and transferred. The basic reproduction number is obtained and used in order to propose ways to control TB in the population. Being a general and adaptable model for different contexts and scenarios, the objective here is to contribute to the understanding of TB dynamics in the population and provide materials that can be used to strengthen TB control strategies. So, this section is structured as follows. First, we present the description of the proposed model, then we present its mathematical analysis. Here we show the positivity of the solution, its existence and uniqueness, the computation of equilibrium points (DFE and EE), the basic reproduction number $\mathcal{R}_0$ and the stability of equilibrium points. Some simulations are presented before discussing the results obtained. The concluding remarks finalize this section (4.1).

4.1.2 Model description

We consider a compartmental model with 8 compartments (groups). In the model we consider a population S that is susceptible to contract TB infection. This population can be infected according to a contact rate α and a transmission rate λ. For this, there is a proportion $1-p$ of this population that will be infected and therefore will be part of compartment I, this is a fast progression to the active TB. We note that a susceptible individual can become latent L_e (latent early) following a contact rate α and a transmission rate λ. In this model a latent individual (L_e and L_f) is not yet able to transmit the disease. Latent individual L_e can become L_f (latent late) following a given rate h. A latent L_e can also directly become infectious (able to infect other people) at a rate q, an individual L_f can also become infectious I at a rate w, this is the low progression to the active TB.

In this model, infected and infectious individuals, who are in the I, L_e and L_f compartments can heal spontaneously and move in the compartment R_2 according respectively to the rates σ, g_2 and k_2. They can also heal after treatment process and move in the compartment R_1 according respectively to the rates γ, g_1 and k_1. These healed individuals can be re-infected according to a rate of transmission λ, a contact rate α and a re-infection rate r. Infectious people I, under treatment can also became L_e according to a rate r_1. During the treatment process, there are people who are lost to follow-up, so people who stop treatment (K). These individuals can be re-infected according to a rate r_3. In the model, we consider others people who are transferred to other hospitals for lack of capacity or medication (T). These people can be re-infected at a rate r_2.

Demography is considered in the TB proposed model. We note Λ the rate of recruitment of susceptible individuals S. In the model people can die, for that we consider μ_1 as the rate of natural mortality (not related to TB infection) and μ_2 the rate of mortality linked to TB infection. The Fig. 4.1 presents the TB transmission dynamics between the different compartments of the model.

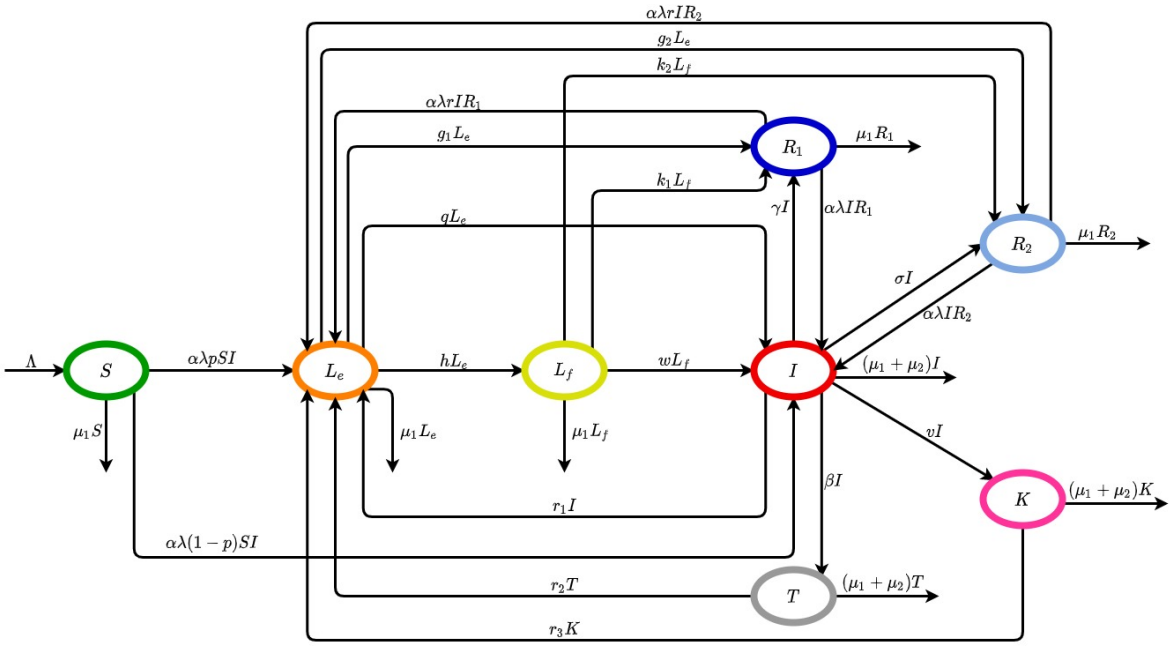


Figure 4.1: Compartmental model of TB transmission

Based on presented information, we obtain the Ordinary Differential Equation System (4.1).

$$\begin{cases} \dot{S} = \Lambda - \alpha\lambda pSI - \alpha\lambda(1-p)SI - \mu_1 S \\ \dot{L_e} = \alpha\lambda pSI + \alpha\lambda rI(R_1+R_2) + r_1 I + r_2 T + r_3 K - \widetilde{B}L_e \\ \dot{L_f} = hL_e - (\mu_1 + w + k_1 + k_2)L_f \\ \dot{I} = wL_f + qL_e - \widetilde{A}I + \alpha\lambda R_1 I + \alpha\lambda R_2 I + \alpha\lambda(1-p)SI \\ \dot{R_1} = g_1L_e + k_1L_f + \gamma I - \alpha\lambda r R_1 I - \mu_1 R_1 - \alpha\lambda R_1 I \\ \dot{R_2} = \sigma I + k_2 L_f + g_2 L_e - \alpha\lambda R_2 I - \alpha\lambda r R_2 I - \mu_1 R_2 \\ \dot{T} = \beta I - (\mu_1 + \mu_2 + r_2)T \\ \dot{K} = vI - (\mu_1 + \mu_2 + r_3)K \\ N = S + L_e + L_f + I + R_1 + R_2 + T + K \end{cases} \tag{4.1}$$

Where $\widetilde{A} = (r_1 + \gamma + \beta + \sigma + v + \mu_1 + \mu_2)$ and $\widetilde{B} = (\mu_1 + h + q + g_1 + g_2)$.

With:

- S : compartment of susceptible people;
- L_e : compartment of early latent TB people, these people are not able to contaminate others ;
- L_f : compartment of late latent TB people, these people are not able to contaminate others ;
- I : compartment of infectious people (active TB), these people are able to contaminate others ;

- R_1 : compartment of healthy people after treatment process and tested;
- R_2 : compartment of spontaneously healthy people and tested ;
- T : compartment of transferred people to another hospital because of missing treatment capacity;
- K: compartment of active TB people who interrupt their treatment;
- Λ : rate of recruitment in compartment S ;
- μ_1 : rate of mortality not related to TB infection ;
- μ_2 : rate of mortality linked to TB infection ;
- γ : rate of recovered after treatment process ;
- σ : rate of spontaneously recovered;
- α : rate of contact ;
- λ : rate of transmission ;
- p : proportion of people;
- β : rate of transferred people in a other hospital;
- v : rate of infected who interrupt their treatment ;
- q : rate of fast progression to active TB, from L_e to I ;
- r : rate of re-infection from R_1 and R_2 to L_e ;
- r_1 : rate of re-infection from I to L_e ;
- r_2 : rate of re-infection from T to L_e ;
- r_3 : rate of re-infection from K to L_e ;
- g_1 : rate of recovered after treatment process from L_e to R_1;
- g_2 : rate of spontaneously recovered from L_e to R_2 ;
- k_1 : rate of recovered after treatment process from L_f to R_1 ;
- k_2 : rate of spontaneously recovered from L_f to R_2 ;
- h : rate of progression of TB infection, from L_e to L_f ;
- w : rate of slow progression of TB infection, from L_f to I ;
- N: represent the total population.

4.1.3 Mathematical analysis of model

In this section, the proposed model is analyzed in order to show the positivity of the solution, the existence and uniqueness of the solution, the calculation of equilibrium points (DFE and EE), the basic reproduction number $\mathcal{R}_0$ and the stability of the equilibrium points.

Positivity of the solution

By adding all the equations. of system (4.1), we have:

$$\begin{aligned}
N =& \Lambda - \alpha\lambda pSI - \alpha\lambda(1-p)SI - \mu_1 S + \alpha\lambda pSI + \alpha\lambda rI(R_1+R_2) + r_1 I + r_2 T \\
&+ r_3 K - (\mu_1 + h + q + g_1 + g_2)L_e + hL_e - (\mu_1 + w + k_1 + k_2)L_f + wL_f \\
&+ qL_e - (r_1 + \gamma + \beta + \sigma + v + \mu_1 + \mu_2)I + \alpha\lambda R_1 I + \alpha\lambda R_2 I - \alpha\lambda r R_1 I \\
&+ \alpha\lambda(1-p)SI + g_1 L_e + k_1 L_f + \gamma I - \mu_1 R_1 - \alpha\lambda R_1 I + \sigma I + k_2 L_f + g_2 L_e \\
&- \alpha\lambda R_2 I - \alpha\lambda r R_2 I \\
&- \mu_1 R_2 + \beta I - (\mu_1 + \mu_2 + r_2)T + vI - (\mu_1 + \mu_2 + r_3)K
\end{aligned}$$

$$N = \Lambda - \mu_1 S - \mu_1 L_e - \mu_1 L_f - \mu_1 I - \mu_1 R_1 \mu_1 R_2 - \mu_1 T - \mu_1 K - \mu_2 I - \mu_2 T - \mu_2 K$$

By simplifying the obtained expression of N, we have $\dot{N} = \Lambda - \mu_1 N - \mu_2(I+T+K)$ with $N = S + L_e + L_f + I + R_1 + R_2 + T + K$. If we consider that there is no disease in the population, we have $N = S$, this implies that $L_e = L_f = I = T = K = R_1 = R_2 = 0$.
By setting $\dot{N} = 0$, we have $\Lambda - \mu_1 N - \mu_2(I+T+K) = 0$, considering $I = T = K = 0$, we obtain:

$$N = \frac{\Lambda}{\mu_1} \tag{4.2}$$

The obtained result (4.2) means that when there is no disease in the population, it is naturally expected that the spread of Tuberculosis in the population will reduce N (that is, $N > \frac{\Lambda}{\mu_1}$). The feasible region of the model system (4.1) is

$$\Omega_\epsilon = \{(S, L_e, L_f, I, R_1, R_2, T, K) \in \mathbb{R}_+^8,\ 0 \leq N \leq \frac{\Lambda}{\mu_1} + \epsilon\}$$

where ϵ is a positive constant. With regard to the model system (4.1) that describes the TB dynamics in the population, we have the following results,

Theorem 4.1.1. *The compact whole Ω_ϵ is an absorptive and invariant whole which attracts all existing solutions of the model system (4.1) in $\mathbb{R}_+^8$.*

Proof. A Lyapounov-LaSalle function $W(t)$ can be define as: $W(t) = N(t)$ with $N(t) = S(t) + L_e(t) + L_f(t) + I(t) + R_1(t) + R_2(t) + T(t) + K(t)$ satisfies

$$\frac{dW}{dt} = \Lambda - \mu_1 W - \mu_2(I+T+K) \leq \Lambda - \mu_1 W \tag{4.3}$$

Therefore, $\frac{dW}{dt} \leq 0$ for $W > \frac{\Lambda}{\mu_1}$. This implies that Ω_ϵ is a positively invariant whole. By solving (4.3), we obtain $0 < W(t) < \frac{\Lambda}{\mu_1} + W(0)e^{\mu_1 t}$, in which case $W(t)$ has as initial condition $W(0)$. Consequently, as $t \longrightarrow +\infty$, we have $0 \leq W(t) \leq \frac{\Lambda}{\mu_1}$. Then, we can conclude that Ω_ϵ is an attractive whole (set) and this achieves the proof. □

Existence and uniqueness of the solution

The system (4.1) is described by a system of autonomous non-linear first order ordinary differential eqs. It can be rewritten in the following matrix form :

$$\dot{X}(t) = F(X(t)) \text{ where } X(t) = \begin{pmatrix} S(t) \\ L_e(t) \\ L_f(t) \\ I(t) \\ R_1(t) \\ R_2(t) \\ T(t) \\ K(t) \end{pmatrix} = \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \\ x_4(t) \\ x_5(t) \\ x_6(t) \\ x_7(t) \\ x_8(t) \end{pmatrix}$$

F is the function C^∞ on $\mathbb{R}^8_+$ described by :

$$F(X(t)) = \begin{pmatrix} f_1(x_1, \cdots, x_8) \\ f_2(x_1, \cdots, x_8) \\ f_3(x_1, \cdots, x_8) \\ f_4(x_1, \cdots, x_8) \\ f_5(x_1, \cdots, x_8) \\ f_6(x_1, \cdots, x_8) \\ f_7(x_1, \cdots, x_8) \\ f_8(x_1, \cdots, x_8) \end{pmatrix}$$

$$F(X(t)) = \begin{pmatrix} \Lambda - \alpha\lambda x_1 x_4 - \alpha\lambda(1-p)x_1 x_4 - \mu_1 x_1 \\ \alpha\lambda x_1 x_4 + \alpha\lambda r x_4(x_5 + x_6) + r_1 x_4 + r_2 x_7 + r_3 x_8 - \mathcal{A} \\ h x_2 - \mathcal{B} x_3 \\ \omega x_3 + q x_2 - \mathcal{C} x_4 + \alpha\lambda x_5 x_4 + \alpha\lambda x_6 x_4 + \alpha\lambda(1-p)x_1 x_4 \\ g_1 x_2 + k_1 x_3 + \gamma x_4 - \alpha\lambda r x_5 x_4 - \mu_1 x_5 - \alpha\lambda x_5 x_4 \\ \sigma x_4 + k_2 x_3 + g_2 x_2 - \alpha\lambda x_6 x_4 - \alpha\lambda r x_6 x_4 - \mu_1 x_6 \\ \beta x_4 - \mathcal{D} x_7 \\ \upsilon x_4 - \mathcal{E} x_8 \end{pmatrix}$$

Where $\mathcal{A} = \mu_1 + h + q + g_1 + g_2$, $\mathcal{B} = \mu_1 + w + k_1 + k_2$, $\mathcal{C} = r_1 + \gamma + \beta + \sigma + \upsilon + \mu_1 + \mu_2$, $\mathcal{D} = \mu_1 + \mu_2 + r_2$ and $\mathcal{E} = \mu_1 + \mu_2 + r_3$.

and $X(t) = (x_1(t), x_2(t), x_3(t), \cdots, x_8(t))$, as F is of class C^1, therefore locally Lipschitzian on $\mathbb{R}^8_+$, we deduce the existence and uniqueness of the maximum solution to the problem of Cauchy associated to the differential equation (4.1), with the initial condition $(t_0,\ X_0) \in \mathbb{R} \times \mathbb{R}^8_+$.
Moreover, F being of class C^∞, we deduce that this solution is also of class C^∞.

Calculation of equilibrium points

To find equilibria of the system (4.1), we set $\dot{S} = \dot{L_e} = \dot{L_f} = \dot{I} = \dot{R_1} = \dot{R_2} = \dot{T} = \dot{K} = 0$. Considering that $X^* = (S^*, L_e^*, L_f^*, I^*, R_1^*, R_2^*, T^*, K^*)$ is the endemic equilibrium, we have:

$$\begin{cases} \Lambda - \alpha\lambda p S^* I^* - \alpha\lambda(1-p) S^* I^* - \mu_1 S^* = 0 \\ \alpha\lambda p S^* I^* + \alpha\lambda r I^* (R_1^* + R_2^*) + r_1 I^* + r_2 T^* + r_3 K^* - \widetilde{B} L_e^* = 0 \\ h L_e^* - (\mu_1 + w + k_1 + k_2) L_f^* = 0 \\ w L_f^* + q L_e^* - \widetilde{A} I^* + \alpha\lambda R_1^* I^* + \alpha\lambda R_2^* I^* + \alpha\lambda(1-p) S^* I^* = 0 \\ g_1 L_e^* + k_1 L_f^* + \gamma I^* - \alpha\lambda r R_1^* I^* - \mu_1 R_1^* - \alpha\lambda R_1^* I^* = 0 \\ \sigma I^* + k_2 L_f^* + g_2 L_e^* - \alpha\lambda R_2^* I^* - \alpha\lambda r R_2^* I^* - \mu_1 R_2^* = 0 \\ \beta I^* - (\mu_1 + \mu_2 + r_2) T^* = 0 \\ v I^* - (\mu_1 + \mu_2 + r_3) K^* = 0 \end{cases} \tag{4.4}$$

Where $\widetilde{A} = (r_1 + \gamma + \beta + \sigma + v + \mu_1 + \mu_2)$ and $\widetilde{B} = (\mu_1 + h + q + g_1 + g_2)$.

By solving the system (4.4), we obtain two possible equilibria. The first one is $X_0 = (S_0, 0, 0, 0, 0, 0, 0, 0)$, which represents the disease-free equilibrium (DFE) with $S_0 = \frac{\Lambda}{\mu_1}$, and the second one is $X^* = (S^*, L_e^*, L_f^*, I^*, R_1^*, R_2^*, T^*, K^*)$, which represents the endemic equilibrium (EE). For that, we extract $S^*, L_e^*, L_f^*, R_1^*, R_2^*, T^*$ and K^* from the system (4.4) in function of I^* as follow:

By extracting S^*, L_f^*, T^* and K^* from the system (4.4) we obtain:

$$S^* = \frac{\Lambda}{\alpha\lambda I^* + \mu_1} \tag{4.5}$$

$$L_f^* = \frac{h L_e^*}{\mathcal{B}} \tag{4.6}$$

$$T^* = \frac{\beta I^*}{\mathcal{D}} \tag{4.7}$$

$$K^* = \frac{v I^*}{\mathcal{E}} \tag{4.8}$$

The substitution of eqs. (4.5) and (4.6) in the second equation of the system (4.4) yields:

$$\alpha\lambda p \left(\frac{\Lambda}{\alpha\lambda I^* + \mu_1}\right) I^* + \alpha\lambda r I^* (R_1^* + R_2^*) + r_1 I^* + r_2 \left(\frac{\beta I^*}{\mathcal{D}}\right) + r_3 \left(\frac{v I^*}{\mathcal{E}}\right) - \mathcal{A} L_e^* = 0 \tag{4.9}$$

$$L_e^* = \frac{1}{\mathcal{A}} I^* \left[\left(\frac{\Lambda\alpha p\lambda}{\alpha\lambda I^* + \mu_1}\right) + \alpha\lambda r (R_1^* + R_2^*) + r_1 + r_2 \frac{\beta}{\mathcal{D}} + r_3 \frac{v}{\mathcal{E}} \right] \tag{4.10}$$

By inserting (4.6) and (4.5) in the fourth equation of (4.4) we have:

$$w \left(\frac{h L_e^*}{\mathcal{B}}\right) + q L_e^* - \widetilde{A} I^* + \alpha\lambda R_1^* I^* + \alpha\lambda R_2^* I^* + \alpha\lambda(1-p) \left(\frac{\Lambda}{\alpha\lambda I^* + \mu}\right) I^* = 0 \tag{4.11}$$

$$L_e^* = \left(\frac{\mathcal{B}}{wh + q\mathcal{B}}\right) \left[\widetilde{A} - \alpha\lambda R_1^* - \alpha\lambda R_2^* - \alpha\lambda(1-p) \left(\frac{\Lambda}{\alpha\lambda I^* + \mu}\right) \right] I^* \tag{4.12}$$

We equate (4.10) and (4.12) and we obtain:

$$\begin{aligned}&\frac{1}{\mathcal{A}}I^*\left[\left(\frac{\Lambda\alpha p\lambda}{\alpha\lambda I^*+\mu_1}\right)+\alpha\lambda r(R_1^*+R_2^*)+r_1+r_2\frac{\beta}{\mathcal{D}}+r_3\frac{v}{\mathcal{E}}\right]\\&=\frac{\mathcal{B}}{wh+q\mathcal{B}}\left[\widetilde{A}-\alpha\lambda R_1^*-\alpha\lambda R_2^*-\alpha\lambda(1-p)(\frac{\Lambda}{\alpha\lambda I^*+\mu})\right]I^*\end{aligned}\tag{4.13}$$

$$\begin{aligned}\frac{\alpha\lambda r}{\mathcal{A}}(R_1^*+R_2^*)+\frac{\mathcal{B}\alpha\lambda R_1^*}{wh+q\mathcal{B}}+\frac{\mathcal{B}\alpha\lambda R_2^*}{wh+q\mathcal{B}}=&\frac{-1}{\mathcal{A}}\left[\left(\frac{\Lambda\alpha p\lambda}{\alpha\lambda I^*+\mu_1}\right)+r_1+r_2\frac{\beta}{\mathcal{D}}+r_3\frac{v}{\mathcal{E}}\right]\\&+\frac{\mathcal{B}}{wh+q\mathcal{B}}\left[\widetilde{A}-\frac{\alpha\lambda\Lambda(1-p)}{\alpha\lambda I^*+\mu_1}\right]\end{aligned}\tag{4.14}$$

$$\begin{aligned}R_1^*\left(\frac{\alpha\lambda r}{\mathcal{A}}+\frac{\alpha\lambda\mathcal{B}}{wh+q\mathcal{B}}\right)=&\frac{-1}{\mathcal{A}}\left[\left(\frac{\Lambda\alpha p\lambda}{\alpha\lambda I^*+\mu_1}\right)+r_1+r_2\frac{\beta}{\mathcal{D}}+r_3\frac{v}{\mathcal{E}}\right]\\&+\frac{\mathcal{B}}{wh+q\mathcal{B}}\left[\widetilde{A}-\frac{\alpha\lambda\Lambda(1-p)}{\alpha\lambda I^*+\mu_1}\right]\\&-\alpha\lambda R_2^*\left(\frac{r}{\mathcal{A}}+\frac{\mathcal{B}}{wh+q\mathcal{B}}\right)\end{aligned}\tag{4.15}$$

$$\begin{aligned}R_1^*=&\frac{\mathcal{A}(wh+q\mathcal{B})}{\alpha\lambda\mathcal{A}\mathcal{B}+\alpha\lambda r(wh+q\mathcal{B})}\\&\left[\frac{-1}{\mathcal{A}}\left[\left(\frac{\Lambda\alpha p\lambda}{\alpha\lambda I^*+\mu_1}\right)+r_1+r_2\frac{\beta}{\mathcal{D}}+r_3\frac{v}{\mathcal{E}}\right]+\frac{\mathcal{B}}{wh+q\mathcal{B}}\left[\widetilde{A}-\frac{\alpha\lambda\Lambda(1-p)}{\alpha\lambda I^*+\mu_1}\right]\right]\\&-\alpha\lambda R_2^*\left(\frac{r}{\mathcal{A}}+\frac{\mathcal{B}}{wh+q\mathcal{B}}\right)\end{aligned}\tag{4.16}$$

By inserting (4.6) in the fifth equation of (4.4) we have:

$$g_1L_e^*+\frac{k_1hL_e^*}{\mathcal{B}}+\gamma I^*-\alpha\lambda R_1^*I^*(r+1)-\mu_1R_1^*=0\tag{4.17}$$

$$L_e^*=\frac{\mathcal{B}\left(\alpha\lambda R_1^*I^*(r+1)-\gamma I^*+\mu_1R_1^*\right)}{g_1\mathcal{B}+k_1h}\tag{4.18}$$

By inserting (4.6) in the sixth equation of (4.4) we have:

$$\sigma I^*+\frac{k_2hL_e^*}{\mathcal{B}}+g_2L_e^*-\alpha\lambda R_2^*I^*(r+1)-\mu_1R_2^*=0\tag{4.19}$$

$$L_e^*\left(\frac{k_2h}{\mathcal{B}}+g_2\right)=\alpha\lambda R_2^*I^*(r+1)+\mu_2R_2^*-\sigma I^*\tag{4.20}$$

$$L_e^*=\frac{\mathcal{B}\left(\alpha\lambda R_2^*I^*(r+1)+\mu_2R_2^*-\sigma I^*\right)}{k_2h+\mathcal{B}g_2}\tag{4.21}$$

Equating (4.18) and (4.21) we obtain:

$$\left(\frac{\mathcal{B}}{g_1\mathcal{B}+k_1h}\right)\left[\alpha\lambda R_1^*I^*(r+1)-\gamma I^*+\mu_1R_1^*\right]=\frac{\mathcal{B}\left(\alpha\lambda R_2^*I^*(r+1)+\mu_2R_2^*-\sigma I^*\right)}{k_2h+\mathcal{B}g_2}\tag{4.22}$$

$$R_1^*=\frac{(g_1\mathcal{B}+hk_1)(\alpha\lambda R_2^*I^*(r+1)+\mu_2R_2^*-\sigma I^*)+\gamma I^*}{(k_2h+\mathcal{B}g_2)(\alpha\lambda I^*(r+1)+\mu_1)}\tag{4.23}$$

Equating (4.16) and (4.23) we obtain:

$$\frac{\mathcal{A}(wh+q\mathcal{B})}{\alpha\lambda\mathcal{A}\mathcal{B}+\alpha\lambda r(wh+q\mathcal{B})}\left[\frac{-1}{\mathcal{A}}\left[\left(\frac{\Lambda\alpha p\lambda}{\alpha\lambda I^*+\mu_1}\right)+\widetilde{Z_1}\right]+\frac{\mathcal{B}}{wh+q\mathcal{B}}\left[\widetilde{A}-\frac{\alpha\lambda\Lambda(1-p)}{\alpha\lambda I^*+\mu_1}\right]\right] - \alpha\lambda R_2^*\left(\frac{r}{\mathcal{A}}+\frac{\mathcal{B}}{wh+q\mathcal{B}}\right)=\frac{(g_1\mathcal{B}+hk_1)(\alpha\lambda R_2^*I^*(r+1)+\mu_2R_2^*-\sigma I^*)+\gamma I^*}{(k_2h+\mathcal{B}g_2)(\alpha\lambda I^*(r+1)+\mu_1)} \tag{4.24}$$

Where $\widetilde{Z_1}=r_1+r_2\frac{\beta}{\mathcal{D}}+r_3\frac{v}{\mathcal{E}}$
From (4.24) we can extract R_2^* and then we obtain:

$$\frac{\mathcal{A}(wh+q\mathcal{B})}{\alpha\lambda\mathcal{A}\mathcal{B}+\alpha\lambda r(wh+q\mathcal{B})}\left[\frac{-1}{\mathcal{A}}\left[\left(\frac{\Lambda\alpha p\lambda}{\alpha\lambda I^*+\mu_1}\right)+\widetilde{Z_1}\right]+\frac{\mathcal{B}}{wh+q\mathcal{B}}\left[\widetilde{A}-\frac{\alpha\lambda\Lambda(1-p)}{\alpha\lambda I^*+\mu_1}\right]\right] - \frac{I^*(g_1\mathcal{B}\sigma+hk_1\sigma+\gamma)}{I^*\widetilde{Z_3}+k_2hu_1+\mathcal{B}g_2u_1}=R_2^*\left(\frac{I^*\widetilde{Z_2}+g_1\mathcal{B}u_2+hk_1u_2}{I^*\widetilde{Z_3}+k_2hu_1+\mathcal{B}g_2u_1}\right)+\alpha\lambda R_2^*\left(\frac{r}{\mathcal{A}}+\frac{\mathcal{B}}{wh+q\mathcal{B}}\right) \tag{4.25}$$

$$\frac{\mathcal{A}(wh+q\mathcal{B})}{\alpha\lambda\mathcal{A}\mathcal{B}+\alpha\lambda r(wh+q\mathcal{B})}\left[\frac{-1}{\mathcal{A}}\left[\left(\frac{\Lambda\alpha p\lambda}{\alpha\lambda I^*+\mu_1}\right)+\widetilde{Z}\right]+\frac{\mathcal{B}}{wh+q\mathcal{B}}\left[\widetilde{A}-\frac{\alpha\lambda\Lambda(1-p)}{\alpha\lambda I^*+\mu_1}\right]\right] - \frac{I^*(g_1\mathcal{B}\sigma+hk_1\sigma+\gamma)}{I^*\widetilde{Z_3}+k_2hu_1+\mathcal{B}g_2u_1}=R_2^*\left(\frac{I^*\widetilde{Z_2}+g_1\mathcal{B}u_2+hk_1u_2}{I^*\widetilde{Z_3}+k_2hu_1+\mathcal{B}g_2u_1}\right)+R_2^*\left(\frac{r\alpha\lambda}{\mathcal{A}}+\frac{\alpha\lambda\mathcal{B}}{wh+q\mathcal{B}}\right) \tag{4.26}$$

Where $\widetilde{Z_2}=(g_1\mathcal{B}\alpha\lambda+g_1\mathcal{B}\alpha\lambda+hk_1\alpha\lambda r+hk_1\alpha\lambda)$ and $\widetilde{Z_3}=(k_2h\alpha\lambda r+k_2h\alpha\lambda+\mathcal{B}g_2\alpha\lambda r+\mathcal{B}g_2\alpha\lambda)$
By highlighting R_2^* we obtain:

$$\frac{\mathcal{A}(wh+q\mathcal{B})}{\alpha\lambda\mathcal{A}\mathcal{B}+\alpha\lambda r(wh+q\mathcal{B})}\left[\frac{-1}{\mathcal{A}}\left[\left(\frac{\Lambda\alpha p\lambda}{\alpha\lambda I^*+\mu_1}\right)+\widetilde{Z_1}\right]+\frac{\mathcal{B}}{wh+q\mathcal{B}}\left[\widetilde{A}-\frac{\alpha\lambda\Lambda(1-p)}{\alpha\lambda I^*+\mu_1}\right]\right] - \frac{I^*(g_1\mathcal{B}\sigma+hk_1\sigma+\gamma)}{I^*\widetilde{Z_3}+k_2hu_1+\mathcal{B}g_2u_1}=R_2^*\left(\frac{I^*\widetilde{Z_2}+g_1\mathcal{B}u_2+hk_1u_2}{I^*\widetilde{Z_3}+k_2hu_1+\mathcal{B}g_2u_1}+\frac{r\alpha\lambda}{\mathcal{A}}+\frac{\alpha\lambda\mathcal{B}}{wh+q\mathcal{B}}\right) \tag{4.27}$$

Then R_2^* is given by:

$$R_2^*=\frac{\widetilde{Z_4}\left[\frac{-1}{\mathcal{A}}\left[\left(\frac{\Lambda\alpha p\lambda}{\alpha\lambda I^*+\mu_1}\right)+\widetilde{Z_1}\right]+\frac{\mathcal{B}}{wh+q\mathcal{B}}\left[\widetilde{A}-\frac{\alpha\lambda\Lambda(1-p)}{\alpha\lambda I^*+\mu_1}\right]\right]-\frac{I^*(g_1\mathcal{B}\sigma+hk_1\sigma+\gamma)}{I^*\widetilde{Z_3}+k_2hu_1+\mathcal{B}g_2u_1}}{\left(\frac{I^*\widetilde{Z_2}+g_1\mathcal{B}u_2+hk_1u_2}{I^*\widetilde{Z_3}+k_2hu_1+\mathcal{B}g_2u_1}+\frac{r\alpha\lambda}{\mathcal{A}}+\frac{\alpha\lambda\mathcal{B}}{wh+q\mathcal{B}}\right)} \tag{4.28}$$

Where $\widetilde{Z_4}=\frac{\mathcal{A}(wh+q\mathcal{B})}{\alpha\lambda\mathcal{A}\mathcal{B}+\alpha\lambda r(wh+q\mathcal{B})}$

In (4.23) we insert (4.28) and we obtain:

$$R_1^*=\frac{(g_1\mathcal{B}+hk_1)(\alpha\lambda\widetilde{Z_5}I^*(r+1)+\mu_2\widetilde{Z_5}-\sigma I^*)+\gamma I^*}{(k_2h+\mathcal{B}g_2)(\alpha\lambda I^*(r+1)+\mu_1)} \tag{4.29}$$

Where

$$\widetilde{Z_5}=\frac{\widetilde{Z_4}\left[\frac{-1}{\mathcal{A}}\left[\left(\frac{\Lambda\alpha p\lambda}{\alpha\lambda I^*+\mu_1}\right)+\widetilde{Z_1}\right]+\frac{\mathcal{B}}{wh+q\mathcal{B}}\left[\widetilde{A}-\frac{\alpha\lambda\Lambda(1-p)}{\alpha\lambda I^*+\mu_1}\right]\right]-\frac{I^*(g_1\mathcal{B}\sigma+hk_1\sigma+\gamma)}{I^*\widetilde{Z_3}+k_2hu_1+\mathcal{B}g_2u_1}}{\left(\frac{I^*\widetilde{Z_2}+g_1\mathcal{B}u_2+hk_1u_2}{I^*\widetilde{Z_3}+k_2hu_1+\mathcal{B}g_2u_1}+\frac{r\alpha\lambda}{\mathcal{A}}+\frac{\alpha\lambda\mathcal{B}}{wh+q\mathcal{B}}\right)} \tag{4.30}$$

By inserting (4.29) in (4.18) we obtain:

$$L_e^* = \frac{\mathcal{B}\left(\alpha\lambda\widetilde{Z_6}I^*(r+1) - \gamma I^* + \mu_1\widetilde{Z_6}\right)}{g_1\mathcal{B} + k_1 h} \tag{4.31}$$

Where

$$\widetilde{Z_6} = \frac{(g_1\mathcal{B} + hk_1)(\alpha\lambda\widetilde{Z_5}I^*(r+1) + \mu_2\widetilde{Z_5} - \sigma I^*) + \gamma I^*}{(k_2 h + \mathcal{B}g_2)(\alpha\lambda I^*(r+1) + \mu_1)} \tag{4.32}$$

By inserting (4.31) in (4.6) we obtain:

$$L_f^* = \frac{h\left(\alpha\lambda\widetilde{Z_6}I^*(r+1) - \gamma I^* + \mu_1\widetilde{Z_6}\right)}{g_1\mathcal{B} + k_1 h} \tag{4.33}$$

We obtain the expressions of $S^*, L_e^*, L_f^*, R_1^*, R_2^*, T^*$ and K^* in function of I^*. Actually, the expression of I^* can be extracted from obtained expressions. Hence, disease-free equilibrium (DFE) and the endemic equilibrium (EE) are found.

Basic Reproduction number

The disease-free equilibrium (DFE) of the system (4.1) is $X_0 = (S_0, 0, 0, 0, 0, 0, 0, 0)$, with $S_0 = \frac{\Lambda}{\mu_1}$. The Jacobian matrix of the system (4.1) at X_0 is

$$J = \begin{pmatrix} -\mu_1 & 0 & 0 & -\frac{\alpha\lambda\Lambda}{\mu_1} & 0 & 0 & 0 & 0 \\ 0 & -\mathcal{Y} & 0 & \frac{\alpha\lambda p\Lambda}{\mu_1} & 0 & 0 & r_2 & r_3 \\ 0 & h & -\mathcal{Z} & 0 & 0 & 0 & 0 & 0 \\ 0 & q & w & -\mathcal{A} & 0 & 0 & 0 & 0 \\ 0 & g_1 & k_1 & \gamma & -\mu_1 & 0 & 0 & 0 \\ 0 & g_2 & k_2 & \sigma & 0 & -\mu_1 & 0 & 0 \\ 0 & 0 & 0 & \beta & 0 & 0 & -\mathcal{B} & 0 \\ 0 & 0 & 0 & v & 0 & 0 & 0 & -\mathcal{C} \end{pmatrix}$$

Where $\mathcal{Y} = (\mu_1 + h + g_1 + g_2 + q)$, $\mathcal{Z} = (\mu_1 + w + k_1 + k_2)$, $\mathcal{A} = ((r_1 + \beta + v + \mu_1 + \mu_2 + \sigma + \gamma) - (\alpha\lambda(1-p)\frac{\Lambda}{\mu_1}))$, $\mathcal{B} = (\mu_1 + \mu_2 + r_2)$ and $\mathcal{C} = (\mu_1 + \mu_2 + r_3)$

Considering just infected compartments as noted in [Van den Driessche and Watmough, 2002], the resulting Jacobian matrix is giving by:

$$J = \begin{pmatrix} -\mathcal{Y} & 0 & \frac{\alpha\lambda p\Lambda}{\mu_1} & r_2 & r_3 \\ h & -\mathcal{Z} & 0 & 0 & 0 \\ q & w & -\mathcal{A} & 0 & 0 \\ 0 & 0 & \beta & -\mathcal{B} & 0 \\ 0 & 0 & v & 0 & -\mathcal{C} \end{pmatrix} \tag{4.34}$$

Writing $J = F - V$ where F contains the new infections in the compartment of infectious individuals. In order to determine F and V we write the system (4.1) as follows:

$$\begin{cases} \dot{L_e} = \alpha\lambda pSI + \alpha\lambda rI(R_1 + R_2) + r_1 I + r_2 T + r_3 K - \widetilde{B} L_e \\ \dot{L_f} = hL_e - (\mu_1 + w + k_1 + k_2) L_f \\ \dot{I} = wL_f + qL_e - \widetilde{A} I + \alpha\lambda R_1 I + \alpha\lambda R_2 I + \alpha\lambda(1-p)SI \\ \dot{T} = \beta I - (\mu_1 + \mu_2 + r_2) T \\ \dot{K} = vI - (\mu_1 + \mu_2 + r_3) K \\ \dot{S} = \Lambda - \alpha\lambda pSI - \alpha\lambda(1-p)SI - \mu_1 S \\ \dot{R_1} = g_1 L_e + k_1 L_f + \gamma I - \alpha\lambda r R_1 I - \mu_1 R_1 - \alpha\lambda R_1 I \\ \dot{R_2} = \sigma I + k_2 L_f + g_2 L_e - \alpha\lambda r R_2 I - \mu_1 R_2 - \alpha\lambda R_2 I \\ N = S + L_e + L_f + I + R_1 + R_2 + T + K \end{cases} \tag{4.35}$$

Where $\widetilde{A} = (r_1 + \gamma + \beta + \sigma + v + \mu_1 + \mu_2)$ and $\widetilde{B} = (\mu_1 + h + q + g_1 + g_2)$

We note $\mathcal{F}_i(x)$ the rates of new individuals in the compartment i, $\mathcal{V}_i^+(x)$ represents the rates that individuals come in the compartment i for any others reasons; $\mathcal{V}_i^-(x)$, represents the rates that individual go out from the compartment i.

We set $\mathcal{V}_i(x) = \mathcal{V}_i^-(x) + \mathcal{V}_i^+(x)$. Considering the system (4.35) we obtain the values of $\mathcal{F}$, $\mathcal{V}^+(x)$ and $\mathcal{V}^-(x)$ as follows:

$\mathcal{F}$ is given by:

$$\mathcal{F} = \begin{pmatrix} \alpha\lambda pSI + \alpha\lambda rI(R_1 + R_2) \\ 0 \\ \alpha\lambda R_1 I + \alpha\lambda R_2 I + \alpha\lambda(1-p)SI \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

$\mathcal{V}^+(x)$ is given by:

$$\mathcal{V}^+(x) = \begin{pmatrix} r_1 I + r_2 T + r_3 K \\ hL_e \\ wL_f + qL_e \\ \beta I \\ vI \\ \Lambda \\ g_1 L_e + k_1 L_f + \gamma I \\ \sigma I + k_2 L_f + g_2 L_e \end{pmatrix}$$

and $\mathcal{V}^-(x)$ is given by:

$$\mathcal{V}^{-}(x) = \begin{pmatrix} (\mu_1 + h + q + g_1 + g_2)L_e \\ (\mu_1 + w + k_1 + k_2)L_f \\ (r_1 + \gamma + \beta + \sigma + v + \mu_1 + \mu_2)I \\ (\mu_1 + \mu_2 + r_2)T \\ (\mu_1 + \mu_2 + r_3)K \\ \alpha\lambda pSI + \alpha\lambda(1-p)SI + \mu_1 S \\ \alpha\lambda r R_1 I + \mu_1 R_1 + \alpha\lambda R_1 I \\ \alpha\lambda r R_2 I + \mu_1 R_2 + \alpha\lambda R_2 I \end{pmatrix}$$

Considering that $\mathcal{V}(x) = \mathcal{V}^{-}(x) - \mathcal{V}^{+}(x)$ we obtain:

$$\mathcal{V} = \begin{pmatrix} (\mu_1 + h + q + g_1 + g_2)L_e - r_1 I - r_2 T - r_3 K \\ (\mu_1 + w + k_1 + k_2)L_f - hL_e \\ \alpha\lambda R_1 I + \alpha\lambda R_2 I + \alpha\lambda(1-p)SI \\ (r_1 + \gamma + \beta + \sigma + v + \mu_1 + \mu_2)I - wL_f - qL_e \\ (\mu_1 + \mu_2 + r_2)T - \beta I \\ (\mu_1 + \mu_2 + r_3)K - vI \\ \alpha\lambda pSI + \alpha\lambda(1-p)SI + \mu_1 S - \Lambda \\ \alpha\lambda r R_1 I + \mu_1 R_1 + \alpha\lambda R_1 I - g_1 L_e - k_1 L_f - \gamma I \\ \alpha\lambda r R_2 I + \mu_1 R_2 + \alpha\lambda R_2 I - \sigma I - k_2 L_f - g_2 L_e \end{pmatrix}$$

Considering only the compartment which contains infected individuals (L_e, L_f, I, T, K) and calculation of the first partial derivative on the DFE at $X_0 = (0, 0, 0, 0, 0, S_0, 0, 0)$ with $S_0 = \frac{\Lambda}{\mu_1}$ we obtain:

$$F = \begin{pmatrix} 0 & 0 & \mathcal{Q} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \mathcal{G} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

Where $\mathcal{Q} = \frac{\alpha\lambda p\Lambda}{\mu_1}$ and $\mathcal{G} = \frac{\alpha\lambda(1-p)\Lambda}{\mu_1}$

For $\mathcal{V}(x)$ we obtain the following result:

$$V = \begin{pmatrix} \mathcal{A} & 0 & -r_1 & -r_2 & -r_3 \\ -h & \mathcal{B} & 0 & 0 & 0 \\ -q & -w & \mathcal{C} & 0 & 0 \\ 0 & 0 & -\beta & \mathcal{D} & 0 \\ 0 & 0 & -v & 0 & \mathcal{E} \end{pmatrix}$$

Where $\mathcal{A} = \mu_1 + h + q + g_1 + g_2$, $\mathcal{B} = \mu_1 + w + k_1 + k_2$, $\mathcal{C} = r_1 + \gamma + \beta + \sigma + v + \mu_1 + \mu_2$, $\mathcal{D} = \mu_1 + \mu_2 + r_2$ and $\mathcal{E} = \mu_1 + \mu_2 + r_3$

By definition, the basic reproduction number $\mathcal{R}_0$ is the spectral radius of the next generation matrix, as follows: $\mathcal{R}_0 = \rho(FV^{-1})$

The eigenvalues of the matrix $\rho(FV^{-1})$ is given by :

$$\left[-\frac{\mathcal{ABDEG}+\mathcal{BDE}\mathcal{Q}q+\mathcal{DE}\mathcal{Q}hw}{\widetilde{Y}},0,0,0,0\right] \tag{4.36}$$

The value of $\mathcal{R}_0$ is the maximum eigenvalue:

$$\mathcal{R}_0=\left|-\frac{\mathcal{ABDEG}+\mathcal{BDE}\mathcal{Q}q+\mathcal{DE}\mathcal{Q}hw}{\widetilde{Y}}\right| \tag{4.37}$$

$$=\frac{\mathcal{ABDEG}+\mathcal{BDE}\mathcal{Q}q+\mathcal{DE}\mathcal{Q}hw}{\widetilde{Y}}$$

Where

$$\begin{aligned}\widetilde{Y}=&\mathcal{ABCDE}-\mathcal{BDE}qr_1-\mathcal{BE}\beta qr_2-\mathcal{BD}qr_3v\\&-\mathcal{DE}whr_1-\mathcal{E}\beta whr_2-\mathcal{D}whr_3v\end{aligned}$$

Stability of equilibrium points

By Theorem 2 in [Van den Driessche and Watmough, 2002], if $\mathcal{R}_0<1$, then the DFE given by X_0 is locally asymptotically stable, but if $\mathcal{R}_0>1$, it is unstable. This leads us to the following theorem:

Theorem 4.1.2. *If $R_0<1$ the disease-free equilibrium X_0 of the system (4.1) is locally asymptotically stable. If $R_0>1$, then X_0 is unstable.*

The proof of Theorem 4.1.2 follows the same steps as Theorem 2 in [Van den Driessche and Watmough, 2002].

We note that the global stability of DFE and EE were observed from simulations and that the mathematical proof was not realized here.

4.1.4 Parameters used in the model

Tab. 4.1 presents the parameters used for simulations. Most of them was taken from the literature and other was fitted based on data at our disposal. The meanings of all parameters are also presented in the Tab. 4.1.

4.1.5 Numerical simulations

In this section, numerical simulations of the proposed TB model are presented. The total population is set at 1000 susceptible individuals. The performed simulations aim to show the stability of the DFE and EE of the system (4.1). The impact of some parameters and groups/compartments of individuals on the dynamics of the TB infection is also presented through numerical simulations.

The EE of the model, $\mathcal{R}_0>1$

In the first simulation we present the actual situation of TB in DRC that is endemic. The stability of the endemic equilibrium (EE), X^*, of the model system (4.1) is presented in Fig. 4.2. Here we simulated the model with $\mathcal{R}_0>1$. The simulation is carried out over several years and attests to the persistence of tuberculosis disease in the population.

Table 4.1: Parameter values and their meanings

Prms	Meaning	Value	Reference	Fitted
Λ	Rate of recruitment ($\Lambda \times N$)	0.0100		Yes
μ_1	Natural death rate	0.0222	[Ozcaglar et al., 2012]	
μ_2	Mortality rate linked to TB	0.040	[Bisuta et al., 2018]	
γ	Recovered rate after treatment (I to R_1)	0.840	[Bisuta et al., 2018]	
σ	Spontaneously recovered rate (I to R_2)	0.250	[Passion-Santé, 2015]	
α	Contact rate	0.0010		Yes
λ	Rate of transmission	0.100	[Adebiyi, 2016]	
$1-p$	Fraction of fast-developing active TB	0.05	[Blower et al., 1995, Zhao et al., 2017]	
β	Rate of transfer to a hospital	0.010		Yes
v	Rate of lost to follow-up	0.030	[Bisuta et al., 2018]	
q	Progression rate (L_e to I)	0.129	[Trauer et al., 2014]	
h	Rate of progression of TB (L_e to L_f)	0.821	[Trauer et al., 2014]	
r	Reinfection rate (R_i to L_e) with i=1,2	0.030	[Blower et al., 1995]	
r_1	Rate of re-infection (I to L_e)	0.63	[Trauer et al., 2014]	
r_2	Rate of re-infection (T to L_e)	0.63	[Trauer et al., 2014]	
r_3	Rate of re-infection (K to L_e)	0.63	[Trauer et al., 2014]	
g_1	Rate of recovered (L_e to R_1)	0.840	[Bisuta et al., 2018]	
g_2	Rate of spontaneously recovered (L_e to R_2)	0.250	[Passion-Santé, 2015]	
k_1	Rate of recovered (L_f to R_1)	0.840	[Bisuta et al., 2018]	
k_2	Rate of spontaneously recovered (L_f to R_2)	0.250	[Passion-Santé, 2015]	
w	Rate of progression (L_f to I)	0.075	[Trauer et al., 2014]	

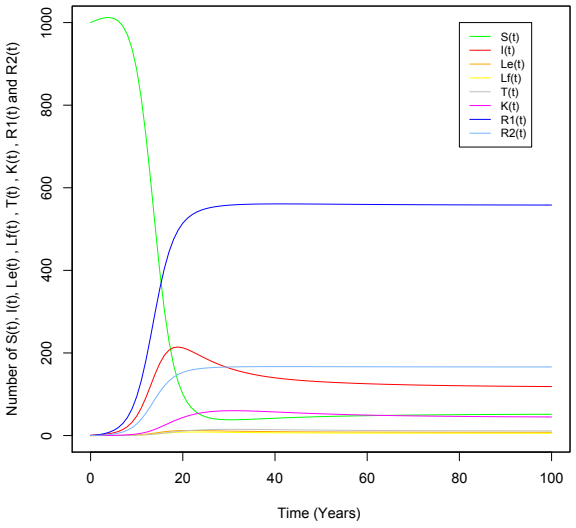


Figure 4.2: Evolution of the model for several years and endemic equilibrium stability using parameters presented in Tab. 4.1 with $\mathcal{R}_0 > 1$. Simulation of the model for $\mathcal{R}_0 = 3.99347$ and $S = 1000$ respectively.

The DFE of the model, $\mathcal{R}_0 < 1$

In the second simulation we present the stability of the DFE, X_0, of the system (4.1). The Fig. 4.3 shows the disease-free equilibrium of the full model. We reduce the rapid progression rate q from L_e (Early Latent) to I (infectious compartment) with the aim of reducing the incidence rate of TB in the population.

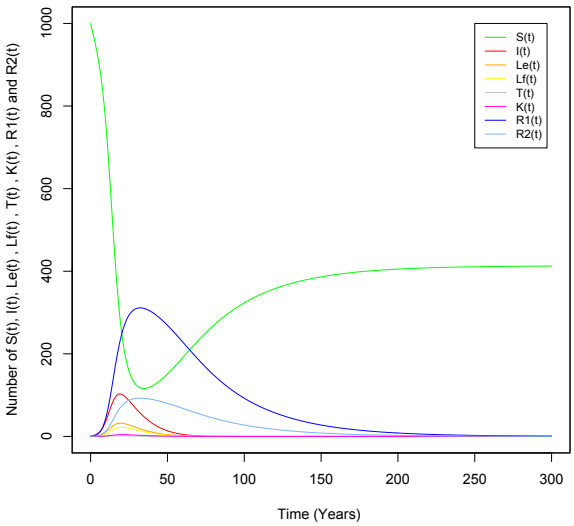


Figure 4.3: Evolution of the model for several years and disease-free equilibrium stability of the model system (4.1) with $\mathcal{R}_0 = 0.68873$ ($\mathcal{R}_0 < 1$). The DFE is reached at the 230th year.

Impact of lost to follow-up and transferred individuals

The third simulation presents the impact of individuals lost to follow-up (K) and transferred (T) on the dynamics of the TB in the DRC population. Figs. 4.4(a) and 4.4(b) show respectively the evolution of the number of infectious individuals over time for several different values of K and T. The Fig. 4.4(c) shows the result of simulation when T and K are considered simultaneously. The Fig. 4.4(d) presents results of simulation with several values of the rate of lost to follow-up.

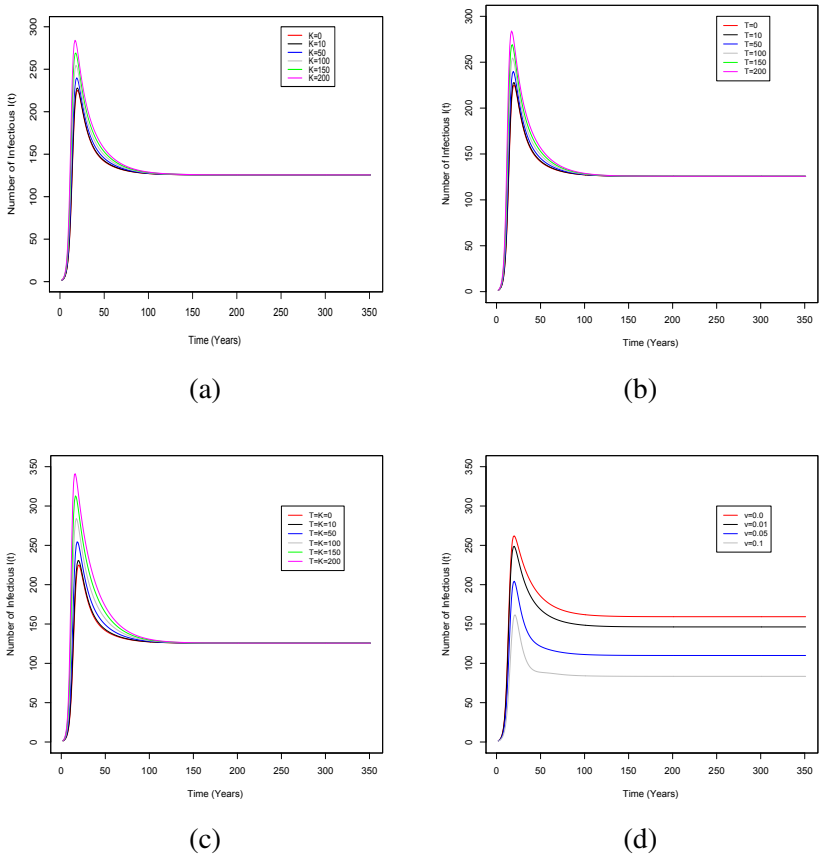
Impact of transmission and contact rates on the disease dynamics

The fourth simulation presents the impact of α and λ on the dynamics of the TB proposed model. By maintaining the value of the rate of transmission $\lambda = 0.100$ as in [Adebiyi, 2016], the simulation will try several values of the rates of contact and we will see its impact on the proposed TB model. Fig. 4.5 shows the results obtained.

4.1.6 Discussion of the results

By considering parameters used (Tab. 4.1), the actual situation of TB in Democratic Republic of the Congo is endemic. Results obtained show that there is at least an endemic equilibrium point because $\mathcal{R}_0 > 1$. Fig. 4.2 with $\mathcal{R}_0 = 3.99347$ shows that the simulation was performed for several years in order to confirm the stability of the endemic equilibrium which implies that the TB will persist in the DRC population according to this condition.

To reach the DFE, DRC health system is called to find mechanism that can help to reduce contamination. The simulation of our mathematical model shows that with certain value of parameters ($\mathcal{R}_0 < 1$), the DFE is globally stable. It means that the tuberculosis will die out in the DRC population. As shown in the Fig. 4.3 we simulate the model for several years to be sure that there is stability of the DFE. To confirm the asymptotically stability of the DFE, we also simulate the model with different several values



(a) (b)

(c) (d)

Figure 4.4: Evolution of the model with $\mathcal{R}_0 > 1$. (a) and (b) present the evolution of the compartment $I(t)$ for several values of K and T for $v = 0.030$ and $\beta = 0.010$. With the same parameters (c) shows the evolution of the compartment $I(t)$ when T and K are considered simultaneously. In (d) there are several values of v considered to see the evolution of I over time.

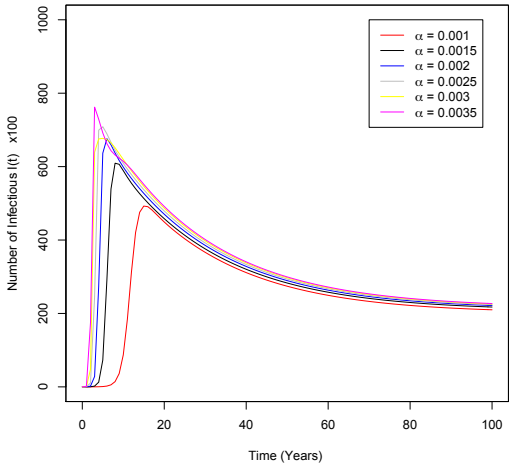


Figure 4.5: Evolution of the model by maintaining the transmission rate of TB $\lambda = 0.100$, we show the result of simulation when $\alpha = 0.0010, 0.0015, 0.0020, 0.0025, 0.0030$ and 0.0035.

of infectious people I. We note that the DFE is reached at 230th year while the model is simulated for several years. Based on the results obtained here, it is clear to see that if the Congolese public health authorities focus on setting up mechanisms that can help to reduce $\mathcal{R}_0$ to a value below 1, pulmonary tuberculosis will be totally eradicated from the Congolese population in the future.

Results obtained show that lost to follow-up and transferred individuals constitute a risk, but less than the cases carrying germs. Rapidly evolving latent/exposures are responsible for the incidence increase in the short and medium term, while slower evolving exposures will be responsible for the persistent long-term incidence and maintenance of TB and delay elimination in the DRC population. Results obtained in Fig. 4.4 show that if some people are lost to follow-up and/or transferred (not followed), the number of these individuals who are untreated has an impact on the incidence of the disease but negligible compared to people with latent tuberculosis. Indeed, if the number of these individuals is high, the results show that the number of new cases of TB increases. By setting the rate of infectious individuals who are lost to follow-up equal to zero, $v = 0$, this means that these people are not followed by health care personnel and therefore remain infectious. The results obtained in Fig. 4.4(d) show that the number of new infected cases is increasing and spreading over several years. This situation means that the individuals lost to follow-up (3% in DRC [Bisuta et al., 2018]) who remain untreated, infect susceptible individuals in the population and then the disease continue to spread in uncontrolled areas. Once the rate of lost to follow-up v is increased, the results show that the number of new cases of infected individuals decreases significantly. In this case, individuals who are lost to follow-up can become Le according to the rate of reinfection r_3. It means that these individuals can be treated and cure according to the rate of recovered. It is consequently important that Congolese public health authorities set up patient monitoring teams in order to reduce the rate of lost to follow-up and transferred (no followed), because these individuals are a permanent danger and constitute the source of TB emergence in DRC population.

The value of the contact rate has a significant impact on the dynamics of TB disease in the population. Fig. 4.5 shows that as the contact rate is high, there are more new cases each year and therefore the severity of infection increases while the recovery rate decreases. These results imply that if the contact rate of infectious people is significantly reduced, this will significantly reduce the incidence of TB in the population. To reduce contamination (parameters α and λ), it will be necessary to strengthen preventive measures, i.e. against contamination. This is where early detection of patient and treatment measures have their major role, because they reduce the number of potential unknwn infected individuals. In addition to these measures, tuberculosis infection control measures include all measures to reduce contact between healthy and infectious people (ventilation of buildings, avoid confinement of patients and wearing masks for caregivers and visitors in the pavilions of tuberculosis patients).

We have presented in this section the analysis and simulation of a compartmental mathematical model of the dynamics of tuberculosis in Democratic Republic of the Congo for a population that incorporates various factors like the lost to follow-up and transferred individuals. The results obtained demonstrate that control lost to follow-up and transferred individuals, monitoring contact, detection of latent individuals and their treatment are actions to be taken to reduce the incidence of the disease and thus effectively control it in the DRC population. This will enable the Congolese authorities in charge of public health to significantly reduce the value of $\mathcal{R}_0$ and move towards a possible elimination of TB in the future. This is the first instance where such analysis is performed in the DRC popultion and therefore improves the preceding ones. It contributes to our knowledge of the spread of this disease, which remains one of the

priorities of the DRC's public health policy agenda. In order to maintain the validity of the proposed model, most of parameters used in this paper was taken from literature, some parameters was estimated based on TB data from DRC. The compartmental model proposed in this paper is well adapted to the reality of the DRC, in the sense that it takes into account groups of individuals who are not generally considered in existing compartmental models. This research provides to the DRC government another way of understanding TB dynamics in the population, which can allow it to improve its unsuccessful TB control. It also gives it necessary materials for fruitful Sustainable Development Goals (SDG) of the United Nations which focus on the global tuberculosis epidemic elimination in 2035. As part of the perspectives, we intend to integrate the consideration of antibiotic resistance into this model. Obtained model should provide solutions in the fight against multi-resistant TB, which, nowadays presents one of the challenges in the fight against TB worldwide [Vinh et al., 2018] and more particularly in Democratic Republic of the Congo.

4.2 MODEL 2: Modeling and simulation of the evolution and control of drug-sensitive (DS-TB) and multidrug-resistant tuberculosis (MDR-TB)

4.2.1 Introduction

According to the WHO report, the number of MDR-TB cases was estimated at about 480,000. Only a part of them is diagnosed and little is put into treatment. This situation remains worrying for the control and even the expected elimination of the disease [Organization et al., 2016]. The overall evolution of the disease shows an increase of approximately 1.5% each year since 2000 [Okuonghae and Ikhimwin, 2016].

Africa, which has only 12% of the world's population [Organization et al., 2016, Nkhoma et al., 2012] has a number of MDR-TB cases estimated at 25% of the global burden. In the continent, the burden is borne by the Republic of South Africa (RSA), Nigeria, Ethiopia, the Democratic Republic of the Congo (DRC) and other countries in the southern region that have high HIV prevalence [Organization et al., 2018a]. The incidence of MDR-TB cases in DRC is therefore very difficult to assess, requiring cohort studies with samples ranging from several hundred peoples to very long periods. Notification of diagnosed cases is a good proxy, especially if the registration system is effective. The data and information collected are subjected to several complex analyses to derive good estimations of the burden [Organization et al., 2015, Organization et al., 2018a].

For DRC, WHO estimated to nearly 210 000 incident TB cases each year, with about 7 000 cases likely to carry MDR-TB bacilli. The reality on the ground is quite different; in 2016 the National Tuberculosis Program (NTP) DRC detected 130,596 cases of tuberculosis and an annual increase in diagnosed cases between 4 and 8%, contrasting with a stationary detection rate of $51[48 - 54]$ or even decreasing [Organization et al., 2016]. A recent study [Bisuta et al., 2018] identified trends in TB screening and treatment and found that a large proportion of patients would be potential reservoirs of MDR-TB and that the proportion of MDR-TB among them would be higher than WHO estimates [Bisuta et al., 2018].

The evolution of a disease in a population depends on several parameters (clinical stages, population movement, different strains of the disease) and mathematical models have gradually emerged as decision support tools for public policy. Indeed, the models allow to predict the consequences in the

population for actions as varied as immunization, screening and treatment [Bentout, , Dowdy et al., 2013]. An interesting approach was that of compartmental models, which divide the population into epidemiological classes such as individuals likely to be infected, those who are infectious, and those who have acquired immunity as a result of healing [Ozcaglar et al., 2012]. Since then, this approach has been used to model many diseases, and continues to be an active research subject taking into account new elements [Bentout, , Goufo et al., 2014, Goufo et al., 2016, Kasereka et al., 2018b, Kasereka et al., 2014, Leon et al., 2017, Ndondo et al., 2016, Atangana et al., 2014, Apollinaire et al., 2016] and to assimilate this evolution, the notion of "basic reproductive number $\mathcal{R}_0$" is used. This key concept is the contribution of mathematics to the theory of epidemics. It is a quantity, the average number of secondary cases generated by an infectious individual during his period of infectivity when he is introduced into a population of named susceptible individuals.

It sould be noted that MDR-TB cases are among the DS-TB individuals who will later develop MDR-TB, these cases cannot be detected by surveillance surveys especially if they are punctual or widely spaced in a population. Mathematical modeling is thus an effective tool for estimating the number of cases [Ozcaglar et al., 2012, Castillo-Chavez and Song, 2004].

Several models have been developed to study the dynamics of MDR-TB, taking into account different parameters. One of the oldest was developed more than 2 decades ago by [Castillo-Chavez and Feng, 1997] and others even more recently having analysed the impact of knowledge of the disease on its progression [Okuonghae and Ikhimwin, 2016], and also the impact of MDR-TB treatment [Trauer et al., 2016]. Most of these models are based on compartmental models developed by John Ross [Bentout,] and adapted by Castillo [Ozcaglar et al., 2012, Castillo-Chavez and Song, 2004]. A model had been developed to estimate the global impact of the Drug Observed Treatment Short (DOTS) strategy predicting the positive evolution of therapeutic success through strict monitoring of drug use.

A combined projection describes 3 possible situations [Ozcaglar et al., 2012, Sharma et al., 2017]:

1. eradication of DS-TB and MDR-TB or elimination of TB as a public health problem;
2. elimination of DS-TB, but persistence of MDR-TB;
3. persistence of both states.

Indeed, in an analysis of the situation of DS-TB and MDR-TB, it was shown that the evolution of the number of DS-TB cases is not always correlated with that of MDR-TB cases, but rather with the outcomes of interventions to control these two entities [Zignol et al., 2016].

There is very rare study that has presented a mathematical model of the evolution of TB in DRC. We recently developed [Kasereka et al., 2019] a model on DS-TB which present the analysis and simulation of a mathematical model of pulmonary tuberculosis transmission with a case study of DRC. Recognizing the absence of an attempt to study the evolution of tuberculosis disease and its fate in relation to the objectives of TB elimination and MDGs achievement, we proposed a compartmental model based on that of Castillo-Chavez [Castillo-Chavez and Song, 2004] and taken up by [Blower and Chou, 2004]. Parameters used in this paper was taken from the literature, from previous studies and other was calculated based on data.

Indeed, we model and simulate the spread and control of DS-TB and MDR-TB in DRC using a two-strain compartmental model. This study should enable us to identify future trends in tuberculosis disease in a resource-limited country, DRC. The basic reproduction number is obtained and used to control this disease in the population. As the proposed mathematical model is adapted to the reality of DRC, the

objective here is to propose to decision-makers some strategies to be implemented for effective control of this disease. The Section! 4.2 is structured as follows. First, we present the construction of the model that gives the description of the model after having presented some basic concepts necessary to understand our research, then we have determined the different parameters of the model, and among them those that most influence the basic reproduction number (sensitivity analysis) and perform simulations for the coming decades. The results obtained are discussed.

4.2.2 Model description

Compartmental model

We consider a model with seven compartments as described in the Fig. 4.6. This figure shows the dynamics of DS-TB and MDR-TB between different compartments.

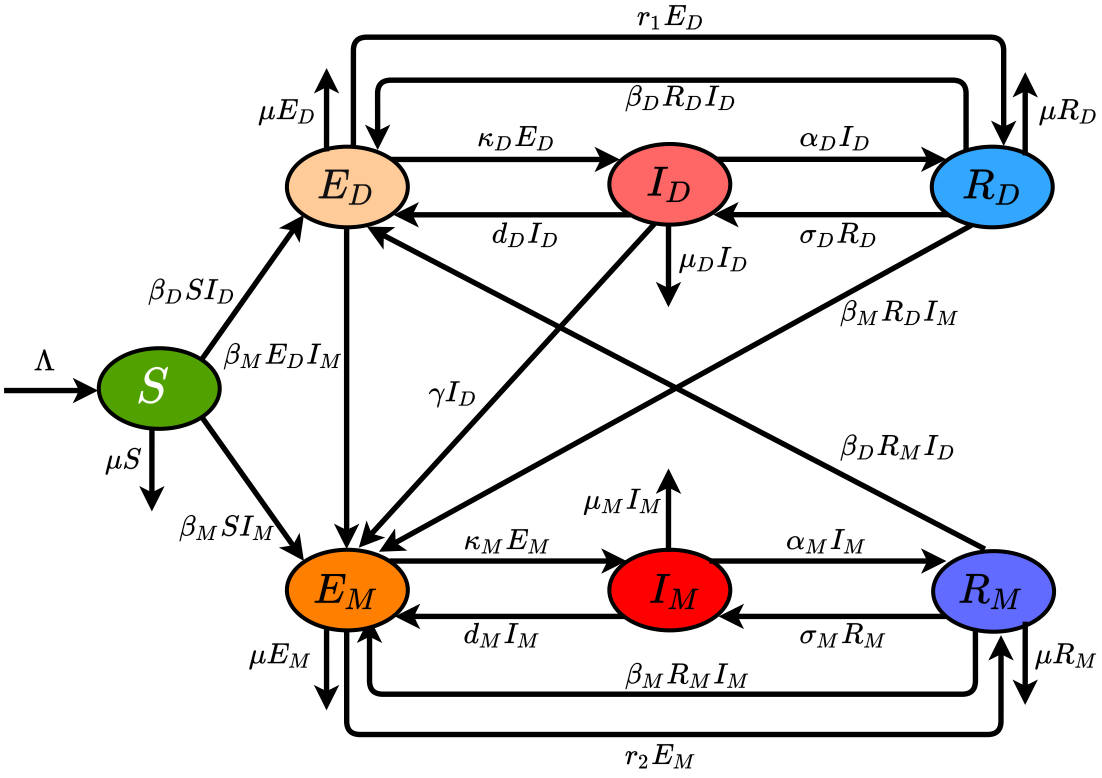


Figure 4.6: Description of the model and its different compartments

Based on these information flows between different compartments, we find the ordinary differential equations 4.38 below:

$$\begin{cases} \frac{S(t)}{d(t)} = \Lambda - \beta_D S(t) I_D(t) - \beta_M S(t) I_M(t) - \mu S(t) \\ \frac{E_D(t)}{d(t)} = \beta_D S(t) I_D(t) - (\mu + k_D + r_1) E_D(t) + d_D I_D(t) - \beta_M E_D(t) I_M(t) + \widetilde{T_1} \\ \frac{I_D(t)}{d(t)} = k_D E_D(t) - (\mu_D + \alpha_D + \gamma + d_D) I_D(t) + \sigma_D R_D(t) \\ \frac{R_D(t)}{d(t)} = r_D E_D(t) + \alpha_D I_D(t) - \beta_D R_D(t) I_D(t) - \mu R_D - \beta_M R_D(t) I_M(t) - \sigma_D R_D(t) \\ \frac{E_M(t)}{d(t)} = \gamma I_D(t) - (\mu + k_M + r_M) E_M(t) + d_M I_M(t) + \beta_M S(t) I_M(t) + \widetilde{T_2} \\ \frac{I_M(t)}{d(t)} = k_M E_M(t) - (\mu_M + \alpha_M + d_M) I_M(t) + \sigma_M R_M(t) \\ \frac{R_M(t)}{d(t)} = r_M E_M(t) + \alpha_M I_M(t) - \beta_M R_M(t) I_M(t) - \mu R_M(t) - \widetilde{T_3} \end{cases} \quad (4.38)$$

Where $\widetilde{T_1} = \beta_D R_M(t) I_D(t) + \beta_D R_D(t) I_D(t)$ and $\widetilde{T_2} = \beta_M R_M(t) I_M(t) + \beta_M R_D(t) I_M(t) + \beta_M E_D(t) I_M(t)$ and $\widetilde{T_3} = \beta_D R_M(t) I_D(t) - \sigma_M R_M(t)$. The entire population is given by $N = S + E_D + I_D + R_D + E_M + I_M + R_M$.

With:

- S : compartment of susceptible people;
- E_D : compartment of latent DS-TB people or exposed to DS-TB;
- I_D : compartment of infectious people (active DS-TB), these people are able to contaminate others;
- R_D : compartment of recovered people from DS-TB ;
- E_M : compartment of latent MDR-TB people or exposed to MDR-TB;
- I_M : compartment of infectious people (active MDR-TB), these people are able to contaminate others;
- R_M : compartment of recovered people from MDR-TB;
- Λ : recruitment rate or population growth;
- μ : mortality rate of the general population;
- β_D and β_M : effective contact rate;
- k_D and k_M: progression rate of latency to infection;
- d_D and d_M : evolution rate of infection to latency;
- α_D and α_M : success rate among screened people;
- r_D and r_M: spontaneous recovery rate from exposed to recovered;
- μ_D : DS-TB death rate;
- μ_M : MDR-TB death rate;
- σ_D and σ_M: relapse rate after treatment;

- γ : proportion of people infected with DS-TB who become exposed to MDR-TB;
- N: represents the total population.

Model parameters

There are several types and sources of parameters. This depends closely on the model proposed by [Dowdy et al., 2013, Castillo-Chavez and Song, 2004, Trauer et al., 2014, Blower and Chou, 2004]. The specific parameters of TB are given by the literature, and concerned the natural evolution of the disease. TB control parameters in DRC, or parameters from epidemiological data are dropped from health reports or previous studies. Also we assumed that control parameters can be adapted or modified following the different types of intervention. Demographic parameters are those derived from the characteristic figures of the general population. Tab. 4.2 presents parameters used in this study.

Table 4.2: Description of the parameters and their annual values

Parameters	Value	Reference
Λ	3.04	[Institut National de la Statistique, 2017]
μ	0.0196	[Ronoh et al., 2016]
β_D and β_M	0.035	[Trauer et al., 2014]
k_D	0.204	[Trauer et al., 2014]
k_M	0.254	[Trauer et al., 2014]
d_D and d_M	0.210	[Trauer et al., 2014]
α_D	0.488	[Bisuta et al., 2018]
α_M	0.072	[Organization et al., 2016]
r_D	0.630	[Trauer et al., 2014]
r_M	0.630	[Trauer et al., 2014]
μ_D	0.04	[Bisuta et al., 2018]
μ_M	0.130	Calculated
σ_D	0.0436	[Bisuta et al., 2018]
σ_M	0.03375	Assumed
γ	0.59	[Bisuta-Fueza1 et al., 2019]

4.2.3 Model analysis

In this section the basic reproduction number is calculated based on the model system (4.38) proposed. $\mathcal{R}_{0D}$ represents the basic reproduction number of DS-TB and $\mathcal{R}_{0M}$ represents the basic reproduction number of MDR-TB. The global $\mathcal{R}_0$ is the maximum between these two basic reproduction numbers. $\mathcal{R}_0$ is defined as the average number of secondary infection cases produced in the whole healthy population by a single infectious individual during the entire period of his effective infectivity.

Positivity of the solution

By adding all the equations of the model 4.38, we have:

$N(t) = \Lambda - \mu D - \mu E_D(t) - \mu_D I_D(t) - \mu R_D(t) - \mu E_M(t) - \mu_M I_M(t) - \mu R_M(t)$

Where $N(t) = S(t) + E_D(t) + I_D(t) + R_D(t) + E_M(t) + I_M(t) + R_M(t)$

Then, $N(t) = \Lambda - \mu N - \mu_D I_D - \mu_M I_M$. When there is no disease in the population ($I_D = I_M = 0$), $N = \frac{\Lambda}{\mu}$, and it is naturally expected that the spread of the disease in the population will reduce N (that is,

$(N > \frac{\Lambda}{\mu})$, the feasible region of the model system (4.38) is

$$\Omega_\epsilon = \left\{(S, E_D, I_D, R_D, E_M, I_M, R_M) \in \mathbb{R}^7_+, 0 \leq S + E_D + I_D + R_D + E_M + I_M + R_M \leq \frac{\Lambda}{\mu} + \epsilon\right\}$$

where ϵ is a positive constant. With respect to model system (4.38), we have the following result:

Proposition

The compact set Ω_ϵ is a positively invariant and absorbing set that attracts all solutions of equation (4.38) *in* $\mathbb{R}^7_+$

Proof

A Lyapounov function

$$V(t) = S(t) + E_D(t) + I_D(t) + R_D(t) + E_M(t) + I_M(t) + R_M(t)$$

satisfies

$$\frac{dV}{dt} = \Lambda - \mu V - \mu_1 I_D - \mu_2 I_M \leq \Lambda - \mu V$$

Hence, $\frac{dV}{dt} \leq 0$ for $V > \frac{\Lambda}{\mu}$. This implies that Ω_ϵ is positively invariant set. On the other hand, solving the differential inequality yields

$$0 < V(t) < \frac{\Lambda}{\mu} + V(0)e^{-\mu t}$$

where $V(0)$ is the initial condition of $V(t)$. Thus, at $t \longrightarrow +\infty$ one has that $0 \leq V(t) \leq \frac{\Lambda}{\mu} + \epsilon$. Then, one can conclude that Ω_ϵ is an attractive set and this achieves the proof.

Disease Free Equilibrium

Among all the possible solutions of equation system (4.38), there is one that is of particular interest to us, namely the solution obtained by assuming that all the infected compartments are empty. i.e., the solution corresponding to the situation where there is no infected individual in the entire population, all individuals are assumed to be healthy [Nkhoma et al., 2012], this is the disease-free equilibrium (DFE). Considering our model, equilibria can be obtained by solving the system of equations (4.38). The disease-free equilibrium is obtained by considering $E_D = I_D = R_D = E_M = I_M = R_M = 0$. This results in the solution $S_0 = \frac{\Lambda}{\mu}; E_D = 0; I_D = 0; R_D = 0; E_M = 0; I_M = 0; R_M = 0$.

This solution corresponds to the disease-free equilibrium (DFE) denoted by $X_0 = (\frac{\Lambda}{\mu}; 0; 0; 0; 0; 0; 0)$. It is clear that in the absence of infection, the entire population $S_0 = \frac{\Lambda}{\mu}$.

Calculation of the basic reproduction number $\mathcal{R}_0$

To calculate $\mathcal{R}_0$, we use the method described by [Carlos-Chavez et al., 2001]. Rewriting the system (4.38) according to the notation in this article, we consider only the compartment witch contain infected individuals. We obtain the transmission matrix noted F presented below:

$$F = \begin{pmatrix} 0 & \frac{\beta_D \Lambda}{\mu} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{\beta_M \Lambda}{\mu} \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

All other transitions to and from the infection subsystem denoted by V represent the transition matrix and is given by:

$$V = \begin{pmatrix} \mu + k_D + r_D & -d_D & 0 & 0 \\ -k_D & \mu_D + \alpha_D + \gamma + d_D & 0 & 0 \\ 0 & -\gamma & \mu + k_M + r_M & -d_M \\ 0 & 0 & k_M & \mu_M + \alpha_M + d_M \end{pmatrix}$$

The inverse of the matrix V is given by:

$$V^{-1} = \begin{pmatrix} \frac{\mu_D + \alpha_D + \gamma + d_D}{\widetilde{A}} & \frac{d_D}{\widetilde{A}} & 0 & 0 \\ \frac{k_D}{\widetilde{A}} & \frac{\mu + k_D + r_1}{\widetilde{A}} & 0 & 0 \\ \frac{\gamma k_D (\mu_D + \alpha_D + d_D)}{\widetilde{A}} & \frac{\gamma(\mu + k_D + r_D)(\mu_M + \alpha_M + d_M)}{\widetilde{A}\widetilde{B}} & \frac{\mu_M + \alpha_M + d_M}{\widetilde{B}} & \frac{d_M}{\widetilde{B}} \\ \frac{\gamma k_D k_M}{\widetilde{A}\widetilde{B}} & \frac{\gamma k_M (\mu + k_D + r_D)}{\widetilde{A}\widetilde{B}} & \frac{k_M}{\widetilde{B}} & \frac{\mu + k_M + r_M}{\widetilde{B}} \end{pmatrix}$$

The product of FV^{-1} is given by:

$$FV^{-1} = \begin{pmatrix} \frac{\beta_D k_D \Lambda}{\mu \widetilde{A}} & \frac{\beta_D \Lambda (\mu + k_D + r_D)}{\mu \widetilde{A}} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ \frac{\gamma \beta_D k_D k_M \Lambda}{\mu \widetilde{A}\widetilde{B}} & \frac{\gamma \beta_M k_M (\mu + k_D + r_D) \Lambda}{\mu \widetilde{A}\widetilde{B}} & \frac{\beta_M k_M \Lambda}{\mu \widetilde{B}} & \frac{\beta_M (\mu + k_M + r_M) \Lambda}{\mu \widetilde{B}} \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

The eigenvalues of the matrix FV^{-1} are given by:
$\lambda_1 = \frac{\beta_M k_D \Lambda}{\mu \widetilde{A}}$; $\lambda_2 = 0$; $\lambda_3 = \frac{\beta_M k_M \Lambda}{\mu \widetilde{B}}$ and $\lambda_4 = 0$.
where $\widetilde{A} = (\mu + k_D + r_D)(\mu_D + \alpha_D + \gamma)(\mu + r_D)d_D$ and $\widetilde{B} = (\mu + k_M + r_M)(\mu_M + \alpha_M + \gamma)(\mu + r_M)d_M$.

Thus, the basic reproduction number $\mathcal{R}_0$ is the spectral radius given by $\mathcal{R}_0 = \rho(FV^{-1})$:

$$\mathcal{R}_0 = \max\{\mathcal{R}_{0D}; \mathcal{R}_{0M}\} \tag{4.39}$$

where

$$\mathcal{R}_{0D} = \frac{\beta_D k_D (\frac{\Lambda}{\mu})}{(\mu + k_D + r_D)(\mu_D + \alpha_D + \gamma)(\mu + r_D)d_D} \tag{4.40}$$

$$\mathcal{R}_{0M} = \frac{\beta_M k_M (\frac{\Lambda}{\mu})}{(\mu + k_M + r_M)(\mu_M + \alpha_M + \gamma)(\mu + r_M)d_M} \tag{4.41}$$

Elasticity or sensitivity indices of the basic reproduction number $\mathcal{R}_0$ with respect to the model parameters

Let X be a variable depending on several parameters $v_1, v_2, ..., v_n$, the sensitivity index $I_{v_i}^X$ of the variable X with respect to the parameter v_i is given by the formula :

$$I_{v_i}^x = \frac{\partial X}{\partial v_i}\frac{v_i}{X} \tag{4.42}$$

where $\frac{\partial X}{\partial v_i}$ is the partial derivative of X with respect to v_i.

The sensitivity index measures the relative change in a state variable X, which results from a relative change in the parameter v_i. Given the explicit formula of the basic reproduction number, we derive the analytical expressions to obtain the sensitivity of this reproduction number, at least from R_{0D} and R_{0M} using equation (4.42).

By considering equation (4.42) and $\mathcal{R}_0 = \max\{\mathcal{R}_{0D}; \mathcal{R}_{0M}\}$, Tabs. 4.3 and 4.4 give the different elasticity indices of $\mathcal{R}_{0D}$ and $\mathcal{R}_{0M}$ with respect to the different parameters of the model. The tables describe the formulas and values of these sensitivity indices in relation to all the system parameters on which the basic reproduction number depend.

Table 4.3: Formulas and values of the sensitivity indices of R_{0D}

Prms	Formula $\frac{\partial R_{0D}}{\partial w} * \frac{w}{R_{0D}}$	Value	Sensitivity indices
β_D	1	0.035	1
r_1	$\frac{-r_D(\mu_D+\alpha_D+\gamma+d_D)}{(\mu+k_D+r_D)(\mu_D+\alpha_D+\gamma)+(\mu+r_D)d_D}$	0.63	-0.87936
k_D	1 - $\frac{(\mu_D+\alpha_D+\gamma)k_D}{(\mu+k_D+r_D)(\mu_D+\alpha_D+\gamma)+(\mu+r_D)d_D}$	0.204	0.76161
γ	$\frac{-\gamma(\mu+k_D+r_D)}{(\mu+k_D+r_D)(\mu_D+\alpha_D+\gamma)+(\mu+r_D)d_D}$	0.59	-0.54493
α_D	$\frac{-\alpha_D(\mu_D+k_D+r_D)}{(\mu+k_D+r_D)(\mu_D+\alpha_D+\gamma)+(\mu+r_D)d_D}$	0.45	-0.42555
d_D	$\frac{-d_D(\mu+r_D)}{(\mu+k_D+r_D)(\mu_D+\alpha_D+\gamma)+(\mu+r_D)d_D}$	0.21	-0.14761
μ_D	$\frac{-\mu_D(\mu+k_D+r_D)}{(\mu+k_D+r_D)(\mu_D+\alpha_D+\gamma)+(\mu+r_D)d_D}$	0.04	-0.03694
μ	$\frac{-\mu[d_D+(\mu_D\alpha_D+\gamma)(2\mu+k_D+r_D)]}{(\mu+k_D+r_D)(\mu_D+\alpha_D+\gamma)+(\mu+r_D)d_D}$	0.0196	0.02445

A negative sensitivity index means that an increase in the value of the parameter leads to a reduction in the value of the variable considered. A positive sensitivity index means that an increase in the parameter value also leads to an increase in the value of the variable considered. In the light of the results obtained and presented in these tables, we find that $\mathcal{R}_0$ is highly sensitive to β (β_S for R_{0S} and β_M for R_{0M}), the rate at which contacts between susceptible and infectious lead to infection. This index being positive, we have only a 10% increase (reduction) of β_S or β_M leads to a 10% increase (reduction) respectively of R_{0S} or R_{0M}. Then comes for R_{0S} the parameter r_1, which represents the healing of people exposed

Table 4.4: Formulas and values of the sensitivity indices of R_{0M}

Prms	Formula $\frac{\partial R_{0M}}{\partial w} * \frac{w}{R_{0M}}$	Value	Sensitivity indices
β_M	1	0.035	1
r_M	$\frac{-r_M(\mu_M^*+\alpha_M+d_D)}{(\mu+k_M+r_M)(\mu_M^*+\alpha_M)+(\mu+r_M)d_M}$	0.072	0.83913
k_M	1 - $\frac{(\mu_M+\alpha_M)k_M}{(\mu+k_M+r_M)(\mu_M+\alpha_M+\gamma)+(\mu+r_M)d_M}$	0.254	-0.83913
α_M	$\frac{-\alpha_M(\mu+k_M+r_M)}{(\mu+k_M+r_M)(\mu_M+\alpha_M)+(\mu+r_M)d_M}$	0.072	-0.20398
d_M	$\frac{-d_D(\mu+r_D)}{(\mu+k_M+r_M)(\mu_M^*+\alpha_M)+(\mu+r_M)d_M}$	0.21	-0.14761
μ_M	$\frac{-d_M}{(\mu+k_M+r_M)(\mu_M+\alpha_M+\gamma)+(\mu+r_M)d_M}$	0.14	-0.36830
μ	$\frac{-\mu[d_M+(\mu_M\alpha_M)(2\mu+k_M+r_M)]}{(\mu+k_M+r_M)(\mu_M+\alpha_M)+(\mu+r_M)d_M}$	0.0196	0.0609

with latent DS-TB, and finally the parameter representing the evolution from latency state to infection. However, it can be observed that for MDR-TB, the parameters that most influence R_{0M} in addition to β_M are first k_M followed by r_M especially relevant to the exposed compartment.

4.2.4 Numerical simulations

In this section, the numerical simulations of the proposed model are presented. The objective of these simulations is to show the dynamics of DS-TB and MDR-TB in the DRC population. The cases of disease-free equilibrium (DFE) and endemic equilibrium (EE) for both types of TB are presented and commented based on the variation of the parameters that influence the baseline reproduction number in Tabs. 4.3 and 4.4.

Disease-free equilibrium for DS-TB and endemic equilibrium for MDR-TB

This simulation shows the evolution of the model when we use the parameters as shown in Tab. 4.2. The performed simulation is presented for several year in order to confirm that the system reach equilibrium of DFE and EE. The Fig. 4.7 presents the performed simulation.

Variation of k_D and k_M by a 50% reduction respectively

By varying the k_D and k_M, the simulation performed shows the result presented in the Fig. 4.8.

Variation of r_D and r_M, simulating latent case treatment

By varying the r_D and r_M, the result is presented in the Fig. 4.9.

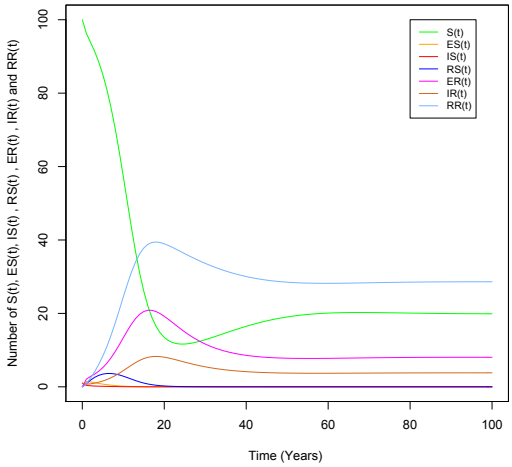


Figure 4.7: A simulation made over 100 years with $S = 100$. The evolution of the disease is dominated by MDR-TB with $R_{0D} = 0.4641$ and $R_{0M} = 4.32321$.

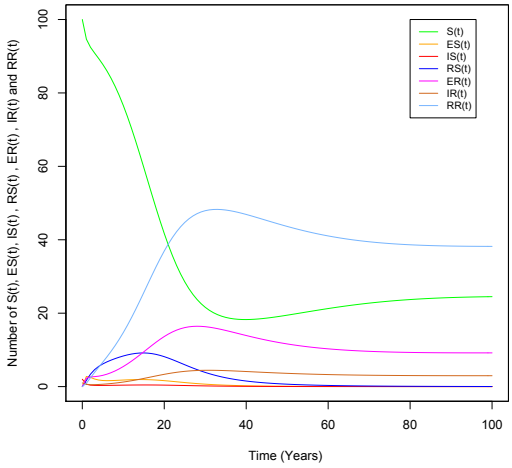


Figure 4.8: This simulation shows a significant reduction in the basic reproduction rate that becomes $R_{0D} = 0.58$ and $R_{0M} = 2.35$.

Variation of α_D and simulation of improvement only in therapeutic success

With the variation of α_D we obtain the results presented in Fig. 4.10.

4.2.5 Discussion of the results

Our objective was to propose a compartmental mathematical model which takes into account both DS-TB and MDR-TB and apply it to DRC's data. The proposed double-strain model is similar to the one proposed in [Castillo-Chavez and Song, 2004] and [Trauer et al., 2014] and served as a basis. Some parameters used were taken from [Bisuta et al., 2018], a study which describe the trends of pulmonary tuberculosis bacteriologically confirmed, treatment outcomes in Democratic Republic of Congo: 2007-2017. The basic

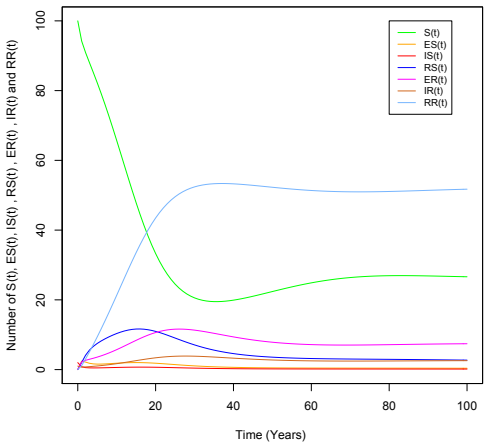


Figure 4.9: Simulation with variation of $r_D = 0.90$, $r_M = 0.80$ and $R_{0D} = 0.78$ and $R_{0M} = 3.41$.

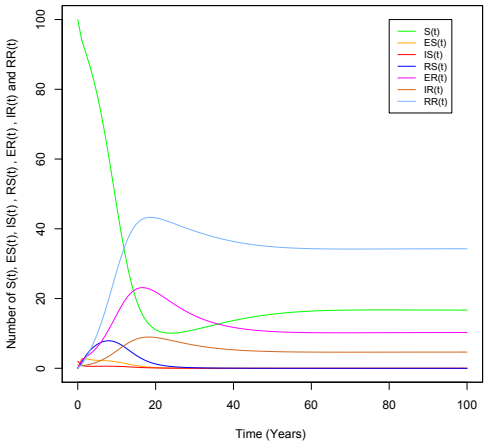


Figure 4.10: We assumed a therapeutic success of 92% for DS-TB cases and 90% for MDR-TB, with screening kept constant in the current values around 50% for TBS and 10% for MDR-TB ($\alpha_D = 0.4692$, $\alpha_M = 0.09$) and $R_{0D} = 1.34$ and $R_{0M} = 2.04$.

reproduction number was calculated for both types of disease and showed us figures that were greater than one and supported the endemic (or endemo-epidemic) progression of TB in general. For MDR-TB, based on the parameters used in this study, we showed that a patient with resistant germ would contaminate at least about 4 people over a 12-month period, in accordance with [Dye, 2008] who had shown an interval of 2.8 to 5.6 people in general. Previous studies have shown us that a patient with MDR-TB can remain for up to 12 months without a drug-resistant diagnosis [Bisuta Fueza et al., 2006] (if molecular testing is not done at the initial TB diagnosis) as shown in Fig. 4.7.

These respective rates show a progression of the tuberculosis endemic with a greater evolution of resistant forms. This shows the great difficulty of achieving TB elimination by 2035; this has also been demonstrated by Sharma et al who have modeled the evolution of DS-TB and MDR-TB in 4 high burden countries, Russia, China, Philippines and South African where they have demonstrated that the

evolution is slower, or even would decline more rapidly for DS-TB and that for MDR-TB the disease will still be persistent for decades, beyond 2040 [Sharma et al., 2017]. The simulation in figs. 4.7 and 4.8 shows similar conditions with a later decline if investments do not increase significantly for the response against this endemic-epidemic set. In practice, this infectivity of TB depends on several factors: the bacillary load of the infectious, promiscuity, duration of contact, stress and immune weakness, etc. [Hickson et al., 2012, Ait-Khaled et al., 1999]. Considering the situation in Fig. 4.10, TB control for its elimination will require transmission reduction actions in all components of the community; infection control measures are represented in this part of the equation. These infection control measures are more easily applied in health facilities in urban areas and populations. Here the community would play a major role in reducing transmission, as the largest number of contagious and undetected patients are found there. This requires major and costly interventions whose financing is difficult to obtain. The parameter that represents the combined factors of screening rates and cure rates in the infectious population $alpha$ showed that a single increase in its value leads to a small reduction in the value of $\mathcal{R}_0$. The cure rate as described in a previous study in DRC; has reached the 90% set by WHO [Bisuta et al., 2018], but detection is still less than 50% [Organization et al., 2016, Organization et al., 2018a]. The influence of the latter is explained by the improvement in the extension of screening and health coverage. In reality, a number of patients who have passed through health facilities have escaped screening either because of staff negligence as described elsewhere or because of insufficient equipment [Bisuta et al., 2018, Trébucq and Schwoebel, 2016], and therefore the use of more sensitive diagnostic methods (tests and algorithms) is justified [WHO, 2017, Falzon et al., 2017, Departement, 2017]. For the MDR-TB component, the improvement would also result from intensified research into MDR-TB among tuberculosis patients and presumed tuberculosis patients through molecular methods [Organization, 2018, Caminero et al., 2013]. However, one model has demonstrated the importance of effective treatment for Uzbekistan, a country with a high burden [Trauer et al., 2016]. The model noted that effective and short, early treatment was a factor in reducing the MDR-TB epidemic. The extension of the time required for diagnosis and/or treatment is one of the factors that is detrimental to reduce the impact of MDR-TB. The same model tested in Papua New Guinea using the short regimen would not have the same impact, the prevalence of the disease would play a major role in this model, in New Guinea the prevalence of DS-TB and MDR-TB being low compared to that of Uzbekistan [Trauer et al., 2016]. This is only true for countries with a high MDR-TB burden where screening has exceeded half of the expected cases. Actually, advances in therapeutic management have made it possible to integrate new molecules that will lead to therapeutic success similar to that of DS-TB [Organization, 2018, End TB Group, 2018]. According to the model developed in this study, the progression of latency to infectious or sick status is the second most important factor that can improve disease control, and this is also recognized in other models [Trauer et al., 2014, Dowdy et al., 2013, Castillo-Chavez and Song, 2004]. In addition, progression to contagious active TB can exacerbate the phenomenon of multiple exposure and re-infection as also described above [Feng et al., 2000], so we must not only focus on actions to detect and treat infectious cases, but also on the phenomenon of repeated contact leading to infection, but above all prevent the progression of latent TB to disease through appropriate strategies [Organization et al., 2018b]. According to this model, the management of latent TB is an important issue; the discussions concern the diagnosis of latent TB and the type of therapy to be applied, which has been addressed elsewhere. This treatment would reduce the progression to infectious status. In DRC, the treatment of latent TB only concerns HIV infected persons and contacts under 5 years

of age who receive isoniazid preventive therapy. This is insufficient to achieve TB elimination within a hundred years.

In Section 4.2 we presented a mathematical model with 7 compartments divided between DS-TB and MDR-TB to understand the dynamics of both drug-sensitive and multi-drug resistant TB in the Congolese population. The results obtained show that with the parameters identified from the current situation, TB in DRC is evolving in an endemic mode with a possibility of later elimination of DS-TB, but with persistence of MDR-TB. Excellent treatment of detected cases, which is the focus of current actions, has a limited influence on achieving TB elimination. But reducing contamination and improve screening and treatment of latent TB are essential actions that can lead to the goals of sustainable development and the elimination of tuberculosis. The strength of this model is that the current limited focus of the NTP on screening and effective treatment is very insufficient to achieve disease elimination. To achieve the elimination level, particular attention must be paid to the situation of latent TB; the complete revision of the guidelines integrating the diagnosis and treatment of latent TB, with an uninterrupted supply of inputs and diagnosis. This involves a study on the prevalence of TB with a particular focus on latent TB by determining the type of strain of origin.

4.3 Conclusion and positioning

The two mathematical models proposed in this chapter provide an understanding of the spread of tuberculosis in the population of the Democratic Republic of the Congo. The analyses made on the differential equations of these models gave us the favour of having an analytical view of the system studied. Indeed, whether it is for the first or second case study, we obtained a result that reflects the overall behaviour of the system. These overall results, however, have allowed us to warn the Congolese government, which acts through its health system.

The difference between these two mathematical models is that MODEL 1 (Section 4.1) focuses on the spread of susceptible TB by considering compartments L_e (early latent TB people), L_f (late latent TB people), T (transfered individuals) and K (lost to follow-up individuals) that are generally not taken into account in the determination of TB incidence and prevalence, whereas MODEL 2 (Section 4.2) is a two-strain compartmental model considering both susceptible and multidrug-resistant TB. Both models are based on real data from the DRC. These two models are interesting and general, therefore they can be applied to pulmonary TB in other countries without major changes.

But we note that the warnings provided here are formulated on the basis of a general behaviour of the system and therefore the influences of the entities (individuals) in exercise are not taken separately. This is one of the limitations of this model because in the case of the spread of a disease, as is the case here, the heterogeneous behaviours of individuals have a considerable impact on the dynamics of the system at both local and global levels. We therefore assume that considering individual behaviours in modeling-simulation of complex systems should improve predictions of the system evolution.

Chapter 5

Agent-Based modeling and simulation of the spread of pulmonary tuberculosis in the population

In this chapter, we propose an agent-based model (named MODEL 3) of the spread of TB in a city. Indeed, this model is based on two population structures. The first one is a mixed population structure with a random contact network, the second one is a 4-level population structure with 4 contact networks. Simulations are performed and results obtained are discussed.

5.1 MODEL 3: Agent-Based model and simulation of the spread of tuberculosis in a mixed population structure

The spread of a disease in a population is not easy to understand because of the large number of interacting entities and elements, as well as its dynamic nature. Since years, transmission of airborne diseases has always been difficult to understand [Kasaie et al., 2013]. However, it is essential to understand how a disease spreads in order to try to eradicate it.

In recent years mathematical models are the most used in epidemiology. However, these classical models obviously have their limits and the basic reproduction number $\mathcal{R}_0$ does not really describe on its own the future of an epidemic in a real population. For example, in real life, most populations have a structure in the form of groups in which relationships between individuals are very close compared to relationships between individuals of different groups. Based on this affirmation, individuals from the same group should be more easily infected. All this requires finer models and the development of the tools necessary for their study. It is here that agent-based models have become necessary. Agent-based modeling is based on intelligent agents. These models are both stochastic and individual. These approaches are interesting because the behavior of each agent is described by an algorithm, they are most realistic. In this approach, the system is more accurate because it is possible to consider an individual level and considering of a geographical representation of interacted entity. The main advantages of this kind of modeling lie in its modularity and incrementality. Modularity allows easy addition or removal of one or more agents. Incrementality means that the theorist can easily improve, refine the agents that his system produce. In a multi-agent approach, the system is more precise and better detailed than a more

comprehensive description that includes an entire population. In addition, multi-agent system modeling is more realistic than the differential equation approach. Indeed, there is a great analogy between this modeling and the systems of cell biology. In other words, in multi-agent systems the level of abstraction is low [Pavé, 1994].

In order to find ways to eradicate tuberculosis in the population, several works was conducted in artificial intelligence especially in multi-agent systems. [Kasaie et al., 2013] implemented an agent-based simulation in a population located in a city. Based on the structure of the 3-level population (household, neighborhood and community), they define a three-layer contact network (close, casual and random contacts). In this model, the dynamics of TB transmission and the role of various contact networks in the spread of tuberculosis have been studied. [De Espíndola et al., 2011] developed an agent-based model (ABM) of the TB transmission and the emergence of drug resistance due to treatment with antibiotics. Based on a mathematical model with 5 compartments proposed by [Blower et al., 1996b] and adopting a specialized structure of the population, the TB transmission was modeled by considering that the transmission can be local and/or global. For this they build an ABM that rely on probabilities to move the agents from one state to another. [Kasaie et al., 2014] constructed an ABM which shows that tracing of household contacts can reduce the incidence of TB in the population and that this could persist for many years after cessation of health policy intervention. Using a bottom-up approach, [Prats et al., 2016] proposed an individual-based model of the dynamics of the pulmonary tuberculosis applied in a constant population. This model shows that population characteristics are crucial for the local epidemiology of the disease. [Tuite et al., 2017] implemented a stochastic agent-based model of tuberculosis transmission in a Canadian indigenous communities. This model projected the incidence of the disease in the absence of additional interventions over 10 years and evaluated different intervention strategies for the control of TB in the region.

In this work, we present a stochastic agent-based model and simulation of the spread of pulmonary tuberculosis in the population located in a province, especialy KATANGA province in DRC. The model is composed by eight groups of individuals which represent eight states of infection of the disease. Our model is based on two population structures. The first is based on a mixed population with a random contact network and the second is based on a 4-levels population (household, direct neighbour, neighbourhood and community) and a contact network of four layers (very close, close, causal and random). The aim here is to provide new ways to understand the dynamics of pulmonary TB in Democratic Republic of the Congo (DRC) by implementing a realistic agent-based model that integrates several groups of people, uses real data and based on a population structure and a contact network close to the real life of the population of the DRC.

This chapter is structured as follows. We first present the TB transmission process, the adopted structure of the population and the network of contacts that will characterize the model. After that, the model description using ODD protocol is presented. Simulations are presented before discussing the results. This chapter is ends with conclusion and positioning.

5.2 A stochastic ABM for TB dynamics

5.2.1 TB transmission process

We develop and simulate a stochastic agent-based model of TB transmission in a city of the Democratic Republic of the Congo. In this model individuals are considered as intelligent agents which can interact among themselves and with their environment. Each agent is located in the simulated environment with related necessary characteristics such us their movements, decision-making, and health states. Parameters used in the proposed model are specific to the city studied, wherever possible or are taken from the literature. The transition between the stages of infection is presented in the Fig. 5.1.

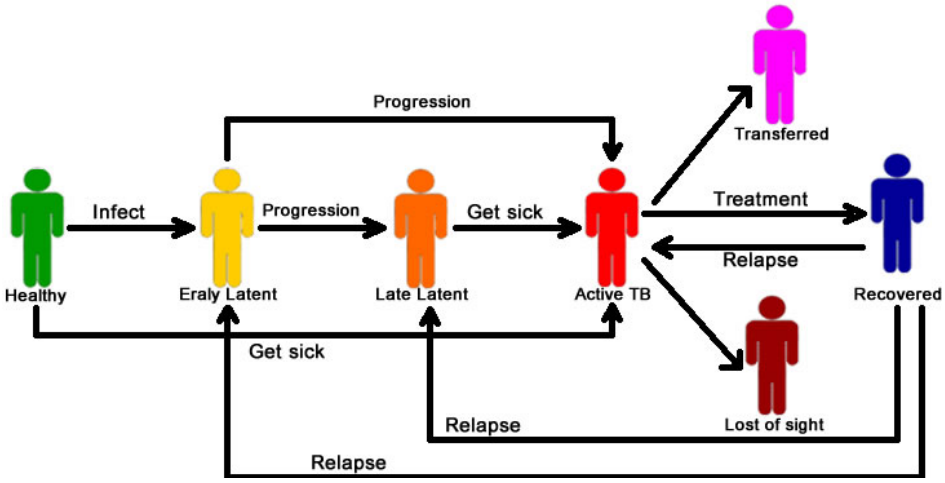


Figure 5.1: Illustration of the state diagram of the model with all states of individuals and all possible transitions.

The model proposed includes eight groups of individuals related to each state of disease transitions. We consider therefore a group S that contents individuals who are susceptible to be affected by the disease. There is a proportion p of individual which will move in a compartment of infectious people noted I or in the compartment of early latent individuals (L_e) according to a probabilities P_{SL_e} given by:

$$P_{SL_e} = (1 - (1 - \lambda)^{n_r}) \tag{5.1}$$

with λ the rate of transmission and n_r represents the number of infectious individuals in the range r of susceptible individuals.

Early latent individuals can move to latent late individuals group (L_f) according to a probability $P(h)$, latent late can become infectious according to a probability $P(w)$. People can heal spontaneously according to a probability $P(\sigma)$ or if they follow a treatment with a probability of therapeutic success of $P(\gamma)$. Recovered individuals may relapse according to a probability equal to $P(r)$. Once relapsed, the recovered probability of that individuals is reduced [Bisuta et al., 2018]. During the treatment process, there are infectious people who interrupt their treatment according to a probability $P(v)$. These individuals are called lost of sight. Due to lack of medication resources, there are some infectious individuals who are transferred to other hospitals, the probability of transfer is $P(\beta)$. It should be noted that, in this model people can die, for that there is a probability of dying linked to TB infection denoted by μ_1 and probability of dying naturally denoted by μ_2.

5.2.2 Population structure and contact networks

Two structures and contact network will be studied. The first one is the mixed population and the second one is a 4-level structure.

Mixed population

We consider a mixed population in a grid that represents a virtual environment. Equation-based models represent this population by subdividing it into homogeneous sub-populations. Each compartment is then quantified and associated with an equation setting out its quantitative evolution. Inter-compartmental interactions are materialized by quantity transfers between the different equations.

It should be noted that, a mathematical model based on differential equations does not represent individuals in a population as properly perceptible entities. It rather represents groups of individuals in terms of population size, as evolutionary quantities. In agent-based modeling, on the other hand, each entity of the population is represented and identified individually with respect to other agents.

This agent-based model, attempts to transform the mathematical model presented in the Section 4.1 (page 66) to the agent-based model. In this model people are on an environment in the form of a grid. People are located in the cells and can be in any state (Susceptible, Early latent, Late latent, Infected, Lost to follow-up, Transferred, Recovered spontaneously, Recovered after treatment) represented by a specific color. There is a radius of contamination between a sick agent and a healthy agent. In this model we define the probabilities of leaving from one state to another (sick to healed, etc.) according to parameters taken from literature. Demography is considered in this model.

In this model, individuals are represented as agents. In the mathematical model, the proportion of susceptible individuals becoming infected depends on the population of infectious persons. In the agent model, the infection of an agent will depend on the number of infected persons who are within its radius of contamination and on a probability of transmission.

A 4-level structure

In order to reproduce the demography of the studied city, we construct a population structure of four levels as presented in Fig. 5.2. Level 1 corresponds to the household and the contact network is very close, level 2 is direct neighbour and the contact network is close, level 3 is neighbourhood and the contact network is causal, and finally the level 4 is the community with the network of contact that is random. A household is composed of people from the same family. In other word, is a group of people sharing the same house and participating in its economy.

The size of the household varies between 1 and 10, and as a discrete triangular distribution of mode equal to 5 individuals as applied by [Kasaie et al., 2013, Kasaie et al., 2014]. This distribution therefore depends on 3 parameters, the first is a minimum denoted by m, the second is a most likely value denoted by n and the last is a maximum denoted by z. Household density is described by the function (5.2).

$$F(x) = \begin{cases} \frac{2(x-m)}{(z-m)(n-m)} & if \quad m \leq x \leq n \\ \\ \frac{2(z-x)}{(z-m)(z-n)} & if \quad n < x \leq z \end{cases} \tag{5.2}$$

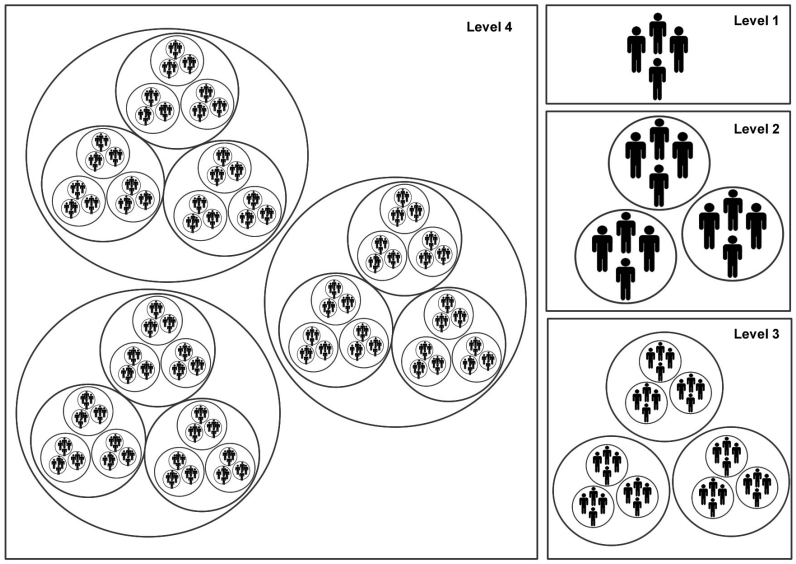


Figure 5.2: Four levels of the population structure and four networks of contact

It should be noted that the values obtained by this probability law are bounded within the interval $[m, z]$.

A parcel is a set of several different households (families). The size of the parcel is taken at random between 1 and 5. A neighbourhood is composed of several parcels that form a network. So, each individual belong to a household, a parcel and a neighbourhood. The city is composed by several neighbourhood (quarters) that represent our simulated environment.

5.2.3 Desccription of the model using ODD protocol

We develop an agent-based model of TB spread using GAMA platform [Grignard et al., 2013]. The implemented model is based on real data from DRC. These data were provided by the National Tuberculosis Control Program of the DRC. Several simulations are presented.

Overview

- **Purpose**: the purpose of the model was to predict over a long period of time the effects of TB patient treatment/management in DRC, and to understand the impact of the contamination radius (environmental configuration) on the spread of TB in DRC.

- **Entities, state variables and scales :** (1) *Agent or Individual*: in the model we consider a single type of agent. Agents represent individuals located in a province (KATANGA). Each agent has state variables as well as characteristics (see Tab. 5.1). (2) *Spatial Units*: each cell represents a space/area on the environment. The state variables of the cells are listed in Tab. 5.2.

- **Environment :** (1) for the mixed population structure, we considered an environment in the form of a 50 x 50 grid. Agents move randomly from one cell to another. Fig. 5.3 presents this environment. (2) for the 4-level structure, the environment is designed using data to determine boundaries of the province. Fig. 5.4 presents this environment. For both population structures, the environment variables in the model include time.

- **Process overview and scheduling :** the model process is in discrete time steps representing 1 year for the mixed population structure and 1 hour for the 4-level population structure. At the beginning of the simulation, individual agents are in any state (Susceptible, Early Latent, Late Latent, Infectious, spontaneously recovered, recovered after treatment, transferred or lost to follow-up). These agents have a probability of leaving from one state to another. At each time step the sub-models are executed (movement, becoming infected, healing, updating of global variables, etc.).

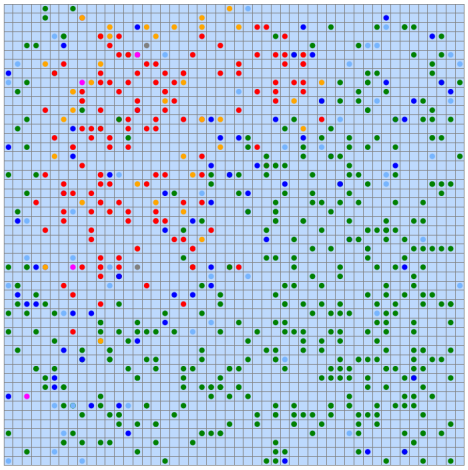


Figure 5.3: Random distribution of agents in a 50x50 grid environment for the discrete agent-based model. Colored dot represent individuals with their specific state (Susceptible: green, Early latent: orange , Late latent: yellow, Infected: red, Lost to follow-up: magenta, Transferred: gray, Recovered spontaneously: lightblue, Recovered after treatment: blue).

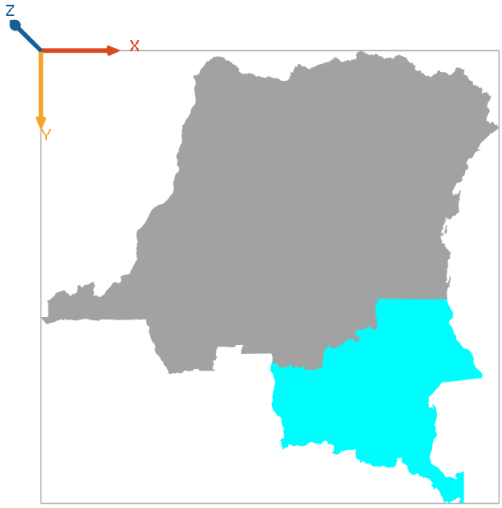


Figure 5.4: Map of DRC (old province configuration), the province of KATANGA is highlighted in GAMA Platform.

Table 5.1: Description of agent state variables

State variables	Description
Agent identifier	Unique agent id
Age	From 0 to 120
Sex	Male, Female
Household identifier	Unique household id and use to connect family members
Susceptible?	Is the agent susceptible?
Early latent?	Is the agent early latent?
Latent late?	Is the agent latent late?
Sick?	Is the agent sick?
Spontaneously recovered?	Is the agent spontaneously recovered?
Recovery after treatment?	Is the agent recovery after treatment?
Transferred?	Is the agent transferred?
Lost to follow-up?	Is the agent lost to follow-up?
Sick days	Number of days the agent has been sick
Early latent days	Number of days the agent has been early latent
Latent late days	Number of days the agent has been latent late
Transferred days	Number of days the agent has been transferred
Lost to follow-up days	Number of days the agent has been Lost to follow-up
Spontaneously recovered days?	Number of days the agent has been spontaneously recovered?
Recovery after treatment days?	Number of days the agent has been recovery after treatment?
Mixed population structure and 4-level population structure	
Location	Determines the location of the agent on the environment
In movement?	Is the agent in movement?
Neighbors	Represents the list of the agent's neighbors
Range of contact	Represents the radius of contamination of the agent. The default is taken between 1 and 5m.
In contact with sick people?	Determine if the agent is in contact with sick people in it range.
4-level population structure	
Adult?	Is the agent an adult? (yes/no)
House	The house where the agent lives
Household type	Couple, couple with children, couple plus others, couple with children plus others, single, single father with children, single mother with children plus others, single mother with children, single father with children plus others, mult1ifamily and other
Household size	Number of agents in household varies between 1 and 10 and follow the discrete triangular distribution of mode equal to 5 individuals. The density of the household is described by the function (5.2).
Couple ?	Is the agent part of a couple? (yes/no)
Children?	Does the agent have children? (yes/no)
Single mother?	Is the agent a single mother (yes/no)
Single father?	Is the agent a single father (yes/no)
Child number	Number of children
Infant	Is the child an infant (yes/no)
Economic status	Economic status of the agent: student, Work, Retired, Unemployed, Looking for First Job, Jobless, Disabled
Job type	Trading, Professional Workers, Managerial and Technical, Non-Manual, Skilled Manual, Semi-Skilled, Unskilled
Work house	House the agent works in
Destination house	The house the agent is moving towards
Contact number	List of the number of contacts an agent has had
Average contacts	The average number of contacts an agent
Contact type	Close, Very close, Causal, Random

Design concept

- **Basic principle**: the spread of the disease is based on a compartimental model that integrates groups of individuals. 8 groups of individuals are considered (Susceptible, Early latent, Latent late,

Table 5.2: Description of cell state variables

State variables	Description
Area identifier	Unique area id
Total agent	The total number of agents in the area
Use	Home, parcel, work, school, town center, community, quartier, residential, commercial, mixed
household	Is there a household here? (yes/no)
House type	Couple, couple with children, couple plus others, couple with children plus others, single, single father with children, single mother with children plus others, single mother with children, single father with children plus others, mult1ifamily and other
Household size	Size of the household on the house
Work size	Number of agents at the workplace
Child age	Age of children in household

Infectious, spontaneously recovered, recovered after treatment, transferred and lost to follow-up). The idea is that when a susceptible agent comes into contact with an infectious agent, it is possible that the susceptible agent may become exposed or infectious according to a certain probability de finined by equation (5.1). (1) for the mixed population structure, agents move randomly over the environment. Their contact structure is also random. (2) for the 4-level population structure, we apply a movement approach in which agents move on routes provided by the province GIS [RGC, 2015]. Agents who do not have a workplace move randomly through the environment. In the weekend the movement of all agents is random.

- **Emergence:** the emergence of the system is justified in the evolution of TB infection in the population. This emergence depends on the type of initially infectious agents, the other agents that come into contact with them along a radius of contamination, the duration of contact but also the frequency of contact.

- **Adaptation:** agents reproduce the behaviours they observe on the basis of a set of rules provided to them. For example (1) in the mixed population structure, if an agent is already cured, he will adapt his behaviour by avoiding contact with infectious agents. (2) for the 4-level population structure, if an agent is infected, he will adapt his behaviour by deciding whether or not to move (to work, to the market, to school, etc.).

- **Sensing:** when moving through the environment, infectious agents can detect susceptible and cured agents. Once cured agents detect infectious agents, these agents avoid contact with them.

- **Interaction:** in this model we assume that agents within the same radius interact with each other and also with their environment. For example, if a susceptible agent is in a same radius with an infectious agent, it is possible that the susceptible agent become contaminated.

- **Stochasticity:** for both population structures, the movement of agents is random. The movement of the agents with their specific states are stochastic. The choice of the destination of all the agents is random. Stochasticity is also in the TB contamination. If a susceptible agent comes into contact with an infectious agent, there is a certain probability that determines whether that agent becomes exposed or directly infectious. In addition, the length of time an agent remains in a

state (Susceptible, Early latent, Latent late, Infectious, spontaneously recovered, recovered after treatment, transferred and lost to follow-up) is randomly chosen.

- **Observation:** data are collected at each execution of the model on individual agents according to their states (Susceptible, Early latent, Latent late, Infectious, spontaneously recovered, recovered after treatment, transferred and lost to follow-up). The output of the model is collected at each time step to observe the evolution of the infectious agents over time. For the 4-level population structure, data on age, marital status and standard of living are collected only if the agents are in a state other than susceptible.

Details

- **Initialization:** (1) for the mixed population structure, agents are randomly placed in the cells. At the beginning of the simulation, the environment has only a given number of susceptible agents and some infectious agents (Chosen by the user).
  (2) for the 4-level population structure, the following initialisations are set:
  - Type is assigned to all households (see all types in Tab. 5.1);
  - Individuals (children and adults) are added to each household according to the type of household.
  - The density of a household is obtained according to the function (5.2);
  - Gender is assigned to individuals in each household;
  - Economic status is assigned to all agents;
  - Agents with economic status are randomly assigned to a work place in the province.

- **Sub-models:**
  - *Timer:* this sub-model manages time in the model. (1) for the mixed population structure, time is modelled in years. (2) For the 4-level population structure, time is determined in hour, day, week, month and year. After every 24 hours, the hour variable is reset to zero and the day variable is incremented by 1. After every 7 days, the day variable is reset to zero and the week variable is incremented by 1. After every 4 weeks, the week variable is reset to zero and the month variable is incremented by 1. After every 12 months, the month variable is reset to zero and the year variable is incremented by 1. We therefore assume a month to 4 weeks (28 days).
  - *Mobility*: (1) for the mixed population structure, agents move from cell to cell on the grid. The choice of destination cell is random.
  - *Contamination:* contamination is based on contact between a susceptible agent and an infectious agent, and the probability of TB transmission. If a susceptible agent is infected then he will change his status from susceptible to exposed (Early latent (L_e) / Latent late (L_f)) or infectious.
  - *Early latent*: An exposed agent (L_e) progresses to (L_f) or to infectious according to a certain probability of progression. The time that the agent will remain in the state L_e before moving to L_f is determined by a certain probability as well.

- *Latent late*: an exposed agent (L_f) progresses to infectious according to a certain probability of progression. The length of time the agent will remain in the (L_f) state before becoming infectious is also determined by a certain probability.
- *Recover:* infectious agents recover based on a probability of spontaneous recovery or a probability of recovery after taking medication.
- *Relapse:* cured agents may relapse and become exposed or infectious based on a certain probability.
- *Lost to follow-up:* when an infectious agent stops taking medication before the end of treatment, it is considered lost to follow-up. Infectious agents become lost to follow-up with a certain probability.
- *Global variables update:* all global variables are updated at the end of each time step. At the same time also the number and percentage of susceptible, exposed (Early latent and Latent late), infected, transferred, lost to follow-up, Recovered (spontaneously and after treatment) agents are all calculated.

5.3 Simulation of the model

5.3.1 Parameters used

Parameters used in this work was taken from literature. Tab. 5.3 presents all parameters, their values and corresponding references.

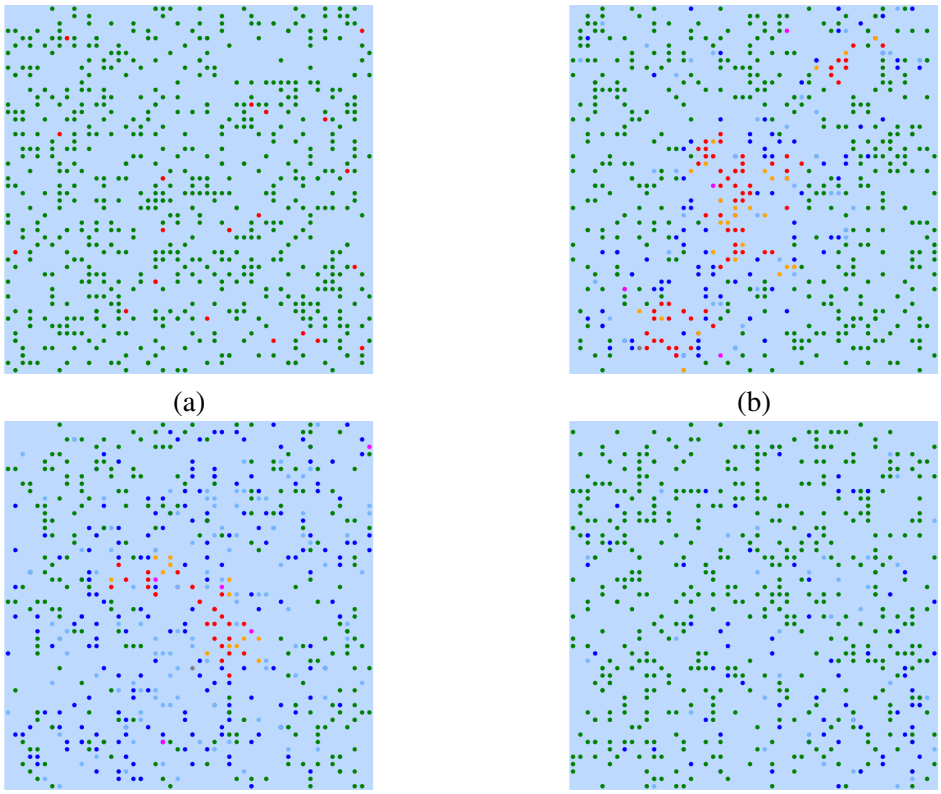
Table 5.3: Description of parameters, their values and references

Prms	**Parameter**	**Value**	**Reference**
μ_1	Natural death rate	0.00222	[Ozcaglar et al., 2012]
μ_2	Mortality rate due to TB	0.040	[Bisuta et al., 2018]
Γ	Recruitement (proportion of the total population)	0.001	Assumed
λ	Probability of transmission (per contact)	0.1	[Abu-Raddad et al., 2009]
β	Rate of tranfert	0.009	Assumed
r	Range of transmission	<=5 m	Assumed
r_1	Probability of relapsing	0.0436	[Bisuta et al., 2018]
h	Probability of early latent to move to latent late individuals' group	0.05	[Abu-Raddad et al., 2009]
σ	Spontaneous recovery rate (per year)	0.1	[Abu-Raddad et al., 2009]
γ	Probability of recovered after treatment (year)	0.84	[Bisuta et al., 2018]
v	Probability of lost to follow-up while on treatment	0.06	[Tuite et al., 2017]
q	Fast progressor (per year)	1.5	[Abu-Raddad et al., 2009]
h	Slow progressor (per year) and Probability of early latent to move to latent late individuals' group	0.05	[Abu-Raddad et al., 2009]

5.3.2 Numerical simulation - Environmement with mixed population

In this work we present two models with different population structures and contact networks. The first one is a mixed population placed on a 50×50 grid with a random contact structure. The second one is a population structure composed of several households with several networks of contacts. This second model is not implemeted here because of the lack of data on the mobility of the Congolese population.

Here we performed simulation for the mixed population structure. Fig. 5.5 presents environment for different time slots.



(a) (b) (c) (d)

Figure 5.5: Mixed population model evolution with N=700, I=20. (a) t=0, (b) t=7, (a) t=25 and (a) t=50. Colored dots represent individuals with their specific state (Susceptible: green, Early latent: orange , Late latent: yellow, Infected: red, Lost to follow-up: magenta, Transferred: gray, Recovered spontaneously: lightblue, Recovered after treatment: blue)

To illustrate results obtained, we performed simulations for the following cases:

- Using basic parameters in Tab. 5.3 and performing simulation without considering the treatment of patients for the first 10 years;
- Varying the radius of contamination of tuberculosis infection in the population.

Consideration of patients treatment from the 11th year

By using basic parameters, we consider that there is no treatment of patients for the first 10 years and we obtain the result shown in the Fig. 5.6.

Variation of the contamination radius

By varying the contamination radius for the values 1, 5, 10 and 15 we obtain the result shown in Fig. 5.7.

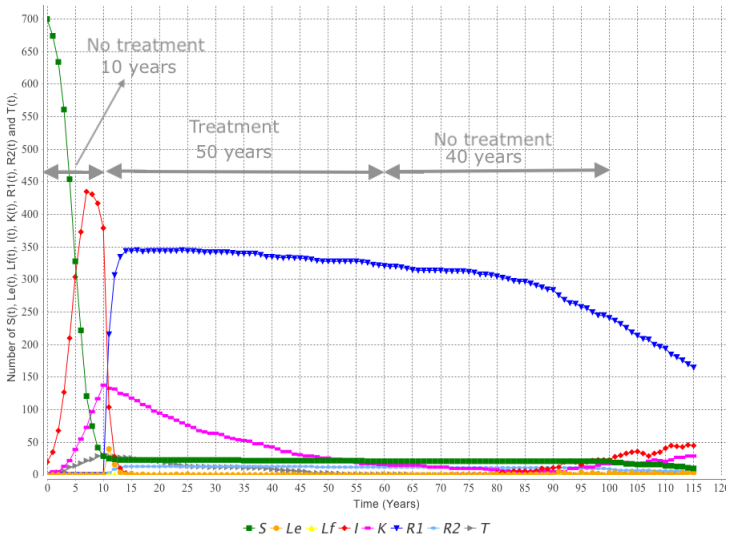


Figure 5.6: Evolution of the model with a mixed population. During the first 10 years infectious and latent individuals are not treated. Treatment starts from the 11th year to the 60th year.

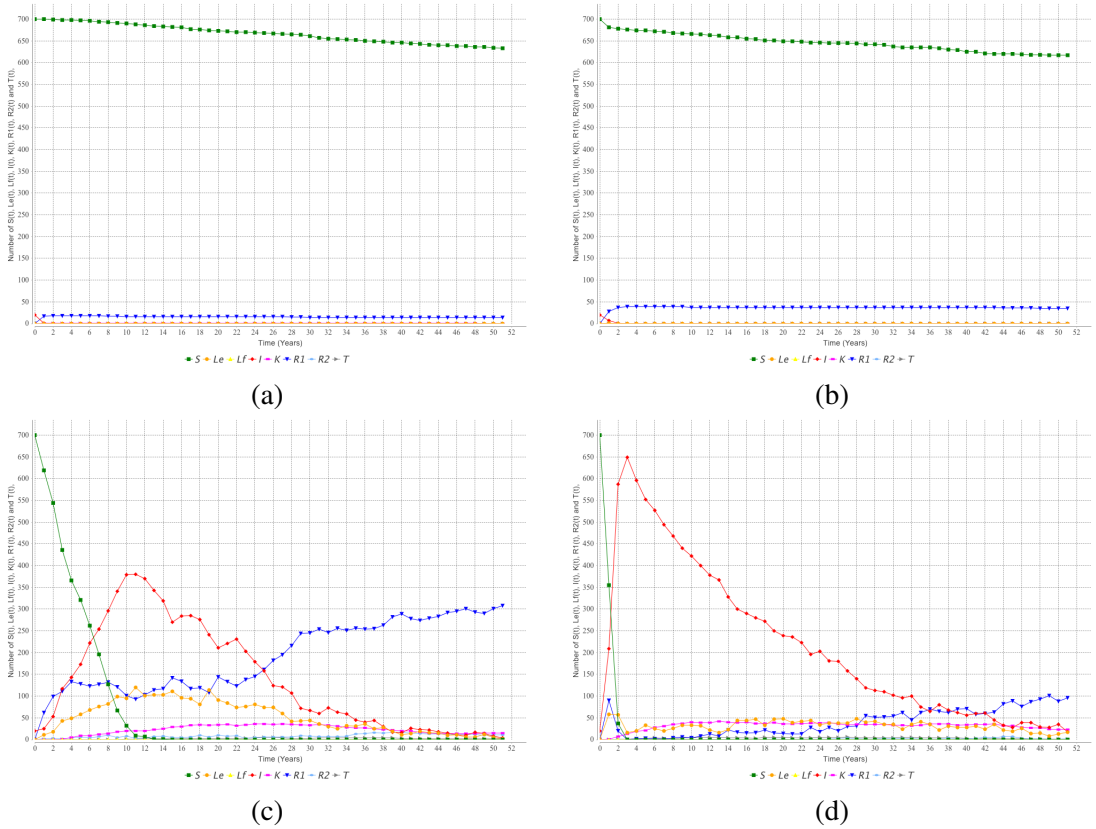


Figure 5.7: Evolution of the model with a mixed population on the grid with a random contact network. Figs. (a), (b), (c) and (d) show the results obtained when the radius of contamination is 1, 5, 10 and 15 respectively.

5.4 Discussion of the results

Nowadays, the success rate of tuberculosis treatment has reached a record level in the world and in DRC in particular (90% or more). As shown in Fig. 5.6, we simulated the proposed model over 10 years without patient treatment, then the treatment of infected and latent persons started in the 11th year up to the 60th year. From the 61st year we stopped treatment again. The result obtained shows that from the 61st year, the population can live for 40 years without patient care before the first case of infection appears.

The variation of radius of contamination has an impact on the incidence of the disease. As shown in Fig. 5.7, if the radius of contamination is large, more people become infected with the disease. In the case of tuberculosis, the state of the environment can influence the radius of contamination since the disease is spread through the air. The results obtained in figs. 5.7(a) and 5.7(b) can be considered as coming from simple environment, while those obtained in figs. 5.7(c) and 5.7(d) can be considered as coming from environments where air conditioning equipment (ventilator, air conditioner, etc.) is used.

The goal of the model presented in Section 5.1 was to develop and simulate an intelligent agent model based on a mathematical model of TB presented previously and to simulate it. Population structures and contact networks were proposed. The simulations performed were based on mixed population structure placed on a grid with a random contact network. Results obtained show that the state of environment can increase the radius of TB contamination and this has an impact on the spread of the disease in the population. The simulations also showed that good patient care strengthens a nation's health system. Indeed, if patients are effectively treated over a long period of time, it is possible that this population may remain free of infection over a long period of time (several years) in the absence of immediate care. This model is particularly interesting because, although it is based on an existing mathematical model, it is capable of capturing many other outcomes that would be complex to achieve if we were to settle for the proportions that the mathematical model based on differential equations would give us.

5.5 Conclusion and positioning

This model has helped to understand the dynamics of tuberculosis in the population. The strong point of this model is that it acts on entities (individuals). Thus, it is easy to follow the evolution of the studied system thanks to the individual characteristics. With this approach, several factors are taken into account, it is easy to track system dynamics from the lowest possible level and see the emergence of new properties at the higher level.

The model implemented here is interesting and general. First, it can be easily applied to understand the dynamics of pulmonary TB in other countries without major changes. Second, it is possible to reuse this model on the spread of other infectious diseases with some changes related to the epidemiology of the disease under consideration.

But, we note that the model needs a lot of details (data on households, their location, the time use of individuals in households, the characteristics of individuals) to have a satisfactory result. This leads to the need in terms of parameters because the model needs a lot of input information, which impacts the cost in terms of hardware capacity. Indeed, the simulation of this model requires a high-capacity computer for a fast execution.

We then assume that coupling this agent-based model to a mathematical model can somehow improve its execution time without altering the results. But this coupling requires many factors to be taken into

account. Indeed, agent-based models act on entities, they are called microscopic. Mathematical models act on a whole population, they are called macroscopic. A compromise will therefore have to be considered so that these two approaches can be combined without problems.

Chapter 6

Hybrid modeling: coupling of Equation-Based Modeling (EBM) and Agent-Based Modeling (ABM)

In this chapter, we propose a novel approach for modeling and simulation of epidemiological systems as complex systems. This proposed approach couples a mathematical model based on differential equations (mathematical) to an agent-based model based on multi-agent systems (artificial intelligence). We apply this modeling-simulation approach to the propagation of TB (MODEL 4) in a multi-scale virtual environment representing several interconnected cities.

6.1 Coupling of models

6.1.1 Introduction

The implementation of a coupled model is not easy because several constraints must be highlighted, particularly in terms of reuse, heterogeneity, interoperability, modularity and differences in spatial and temporal scales [Siebert, 2011].

Nowadays, there is a growing body of work on model coupling approaches, as part of research on the integration of different modeling tools [Duboz, 2004]. With advances in modeling it is becoming difficult to limit a complex model within a uniform design framework, this challenge is pushing many researchers to opt for a multi-platform representation of a heterogeneous system integrating hybrid or mixed solutions [Villa, 2001]. The aim here is to enrich the modeling experience and to have a better understanding of the complex systems studied, in particular the system for the spread of infectious diseases.

Apart from the definitions of the basic concepts, this chapter outlines the above-mentioned constraints and shows how other works propose to address them by presenting it at several levels: the conceptual level, the semantic level, the syntactic level, the dynamic level and the technical level [Tolk and Muguira, 2003].

The integration of heterogeneous formalisms and different levels of abstraction into the dynamics makes it possible to capture the natural complexity of the system to be modeled. To achieve this, it is important to take into account the simultaneous interinfluence of several models [Capera et al., 2003]. This is why we are currently witnessing a trend in modeling coupling that is attempting to gradually

replace uniform, unique and homogeneous models. In this section a review of existing model coupling approaches, their classifications, advantages and limitations are presented. The aim here is to see how in existing work questions on coupling approaches have been addressed.

6.1.2 Definitions of the terms

The term "coupling" comes from the verb "to couple". In modeling-simulation, coupling consists in defining how the models, each representing a particular dynamic of the complex system to be modelled, will be associated. This is a special case of modeling. Unlike "classical" modeling, which creates only one model, model coupling represents the dynamic system through a set of models to create the multi-model [Zeigler and Ören, 1986, Fishwick and Zeigler, 1992]. Coupling is defined as having at least two interacting models that can operate independently [Fianyo, 2001]. Model coupling can be adopted in many cases, especially when the problem to be modelled requires several levels of detail to be taken into account (when the process under study is active in a very heterogeneous region, for example) and the best model approaching the system is an association of different ones. Here the objective is to couple different process models that solve the same question with different levels of detail. This coupling approach can also be considered when the question to be answered is a global question (the process to be studied is the result of a tangle of processes).

Model coupling is a problem that arises when dealing with complex issues and where the speed of design of new products is an important issue, particularly in industrial, ecological and other environments. [Fianyo, 2001]. Thus, the study of the dynamics of infectious diseases in a population at different scales is a good example of a complex system that shows the value of coupling in the integration and interaction between different social factors such as demography, economy, standard of living, behaviour, etc.

6.1.3 Advantages of coupling

Several advantages can be considered [Fianyo, 2001]:

- Coupling allows experts from different disciplines to build a model with theoretical materials that have not always been designed for use together;
- The coupling of the models increases the descriptive power of the model and allows to have another view on the system, hoping at the same time a lower risk of error and a faster construction of the simulation model;
- It makes it possible to capitalize on models;
- The use of multiple models facilitates the interaction between parameters and system actors and allows processes to run with different time steps and levels of abstraction;
- Facilitates the reproduction and validation of results.

But it should be noted that the reuse of models is limited by the need to rewrite or encapsulate the models in order to be able to couple them.

6.1.4 Types of coupling

Coupling methods are classified according to the degree of coupling between models and the way in which interactions between coupled models take place. In this work, five forms of coupling are presented:

Weak coupling

A coupling is said to be weak or loose when the models remain independent and the exchange between the coupled models is done via unidirectional data transfers where the results of one model are used as input (as parameters) to a second model. In this type of coupling, only the data are exchanged, but the models remain independent of each other. These couplings are generally static and only allow the representation of the initial and final states of the coupled models. However, we note that the memorization of the intermediate states is possible. These states can be either periodically or during events of particular interest during the execution session [Zunga et al., 1998]. This poses the problem of dynamically changing and visualizing the model execution parameters during simulation. Fig. 6.1(a) illustrates this type of coupling.

Strong coupling

This type of coupling, also called close coupling, involves the presence of a database that the models share through an interface module that manages the integrity of the data used by the models. These models both influence each other through massive dynamic data exchanges despite their independence. This coupling ensures the dynamic visualization of system changes thanks to the database common to the coupled models [Hassoumi, 2015]. However, the implementation of these features requires redundant developments in an unsuitable environment [Hassoumi, 2015]. Fig. 6.1(b) below illustrates this type of coupling by showing the interaction between the models and the common database.

Mean coupling

This type of coupling, also called parallelisassions, is generally used to couple computer models with mathematical models [Kant, 2012]. This coupling is frequently used in work that deals with complex phenomena, where the mathematical model helps to calibrate the data in the computer model for optimization purposes, for example, and to validate it through statistical analyses, for example. Fig. 6.1(d) below illustrates this type of coupling.

Integral coupling

This type of coupling, also called hierarchical coupling, is a type of coupling in which the models are modified to be adapted to each other and to ensure the perfect coupling. In this type of coupling, all the resulting models form a single super-model rewritten from several models [Hassoumi, 2015] as illustrated in Fig. 6.1(e).

Cooperative coupling

This type of coupling meets the limits of close coupling. This coupling can be direct or indirect. It is said to be direct cooperative when the two models remain independent and use a client/server link to interact as shown in the Fig. 6.1(c). When the compatibility of the models can be supported by a median system, we refer to indirect cooperative coupling [Maillé and Espinasse, 2005, Hassoumi, 2015].

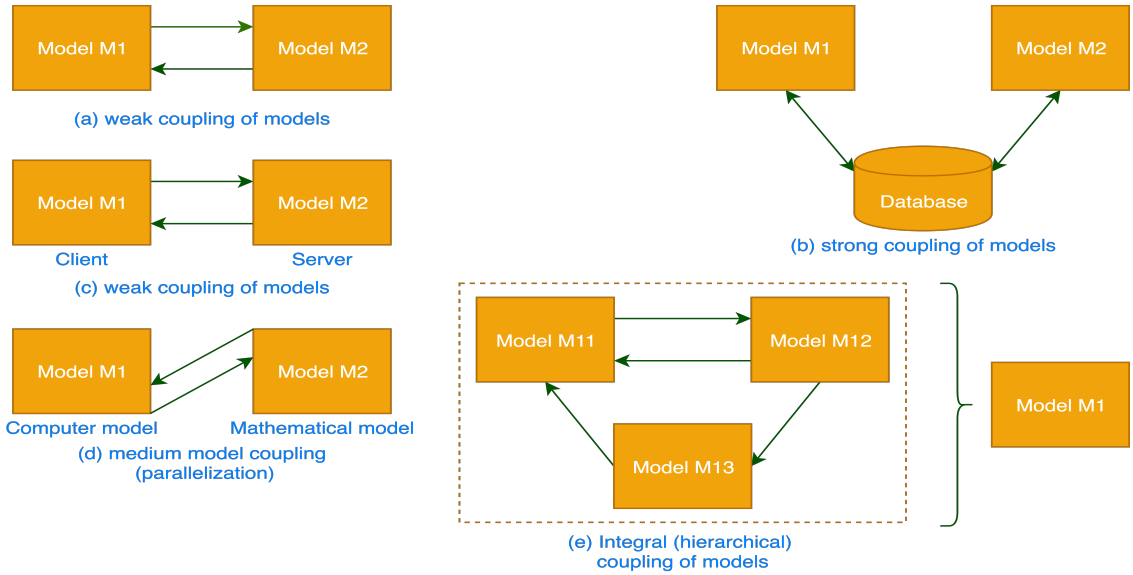


Figure 6.1: Types of model coupling [Hassoumi, 2015]

6.1.5 Coupling constraints

The types of coupling presented above raise some difficulties that need to be managed. In this work we present these constraints as in the work of [Hassoumi, 2015]:

Reuse of models

Nowadays, several models exist in the literature, these models would undoubtedly be interesting to reuse to model other phenomena. If we are to apply the notion of coupling, these models are not necessarily designed to receive or send data to other models. Hence their direct coupling can be difficult to undertake. In most cases, the reuse of models will require rewriting or encapsulation of the models to be able to couple them. It is therefore important to plan a minimum of modifications to be made on the models in order to correlate them with others in order to achieve a successful coupling [Hassoumi, 2015].

Modularity

When the different elements that make up a product have been designed independently, but work together as a homogeneous whole, we are dealing with a complex product called modular [Helper et al., 2002]. Modeling complex systems often requires model changes to facilitate system transformation. In a coupling process, the modeler must be able to choose between several models existing in the literature. Modularity is a constraint that must therefore be taken into consideration in order to easily change the elementary models to be coupled [Hassoumi, 2015].

Interoperability

The term interoperability aims to allow several heterogeneous sources of information to share and control data exchanges. Indeed, the advantage of reusing models in the literature is to revalue the existing ones but does not allow to choose the formalism and paradigms used in these models. It will therefore be

necessary to make different models interact in a synchronized and simultaneous way when establishing communication channels between the models. As part of the coupling, these interactions can take place according to a federated schema of the database or through mediators responsible for controlling access and resolving conflicts between data from different sources [Hassoumi, 2015].

Heterogeneity

When the system to be modelled has several heterogeneous representations, this can pose problems when applying the concepts of model coupling. Indeed, the models used in the coupling process use different languages and different formalisms to manipulate their input and output variables. We are therefore confronted with the problem of coherence between various representations that relate to the same concept. To ensure the compatibility of formalisms, it is often necessary during coupling to apply transformations in advance on the parameters and their measurement units to translate them into representation systems that the models can manipulate and share [Fianyo, 2001].

Difference in model scales

The modeling of certain dynamics sometimes requires the use of several models representing different components of the complex system under study that evolve at different spatial and temporal scales [Hassoumi, 2015]. It is therefore necessary to be able to manage these differences in scales in order to have a consistent coupling and results. In the context of this work, this constraint was addressed. To address these difficulties, it is important to structure the coupling approach on different levels, from low-level coupling to more elaborate coupling where the dynamics of exchanges between models integrates the semantic, dynamic, technical and other dimensions.

6.2 Coupling of EBM and ABM with application to the TB dynamics

In this section we present a hybrid stochastic metapopulation model for controlling the spread of tuberculosis in a multi-scale virtual environment. In the model population moves from city to city using an agent-based model while the spread of the disease in each city is managed by solving a differential equation of TB dynamics according to a compartmental model. Numerical simulations of the model are carrier out using GAMA platform [Grignard et al., 2013].

6.2.1 MODEL 4: A hybrid stochastic metapopulation model for controlling the spread of tuberculosis in a multi-scale virtual environment, application to tuberculosis dynamics in DRC

A. Introduction

In recent years, compartmental mathematical models such as SIS, SIR, SEIR, etc. have been the most widely used to control and understand the dynamics of infectious diseases in populations [Goufo et al., 2014, Kasereka et al., 2014, Trauer et al., 2014, Atangana et al., 2014, Goufo et al., 2016, Zhao et al., 2017]. However, the concrete application of these models to environments that require the consideration of individual mobility is not easy [Landy and Vinh, 2013]. It is true that metapopulation models have emerged. These

models consider that populations of the same species are spatially distributed and that there are more or less regular and important exchanges of individuals between these populations [Hanski et al., 1997]. The habitat of this metapopulation is an ecological unit corresponding to the landscape, i.e. a set of sites with various stages of ecological succession and whose geography allows limited gene exchanges but existing from one site to another. In general, metapopulation processes emerge within a population of individuals as a result of the spatial fragmentation of their habitat. These models have increased their weakness with regard to its mobility component, which is treated in an aggregate manner, and therefore do not consider the heterogeneous behaviors of individuals.

In this work, we propose a hybrid stochastic metapopulation model in which a compartmental mathematical model of tuberculosis is coupled to an agent-based model. Indeed, individuals are placed in cities in which the dynamics of the disease is managed by solving the differential equation system by the Runge Kuta method applied by [Kasereka et al., 2014] and individuals move between several cities over a circle using an agent-based model. Simulations of the hybrid model proposed are performed and the impact of population mobility on the spread of the disease is assessed.

This work is structured as follows. We present the description of the proposed model and then show the assumptions considered in this work. The definition of the considered virtual environment is also presented. Some simulations of the model are presented before discussing the results obtained.

B. Description of the mathematical model

We use here the mathematical model proposed in Chapter 4. The mathematical analysis of the model is presented in thie same Chapter. The Fig. 6.2 presents the compartmental model of TB transmission considered.

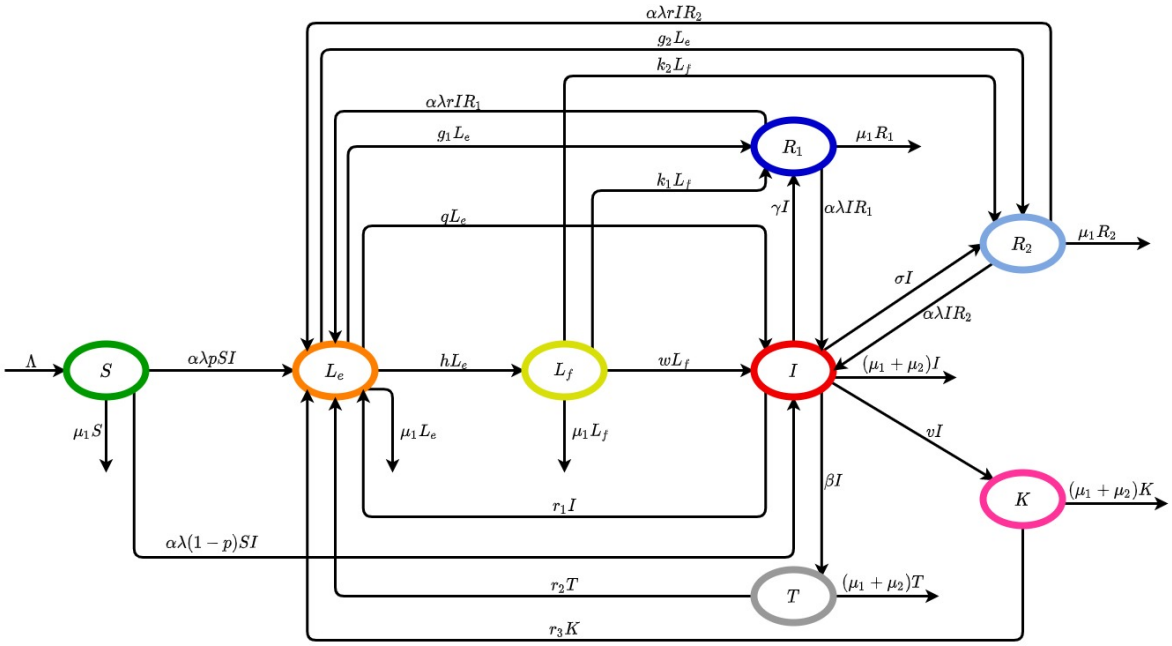


Figure 6.2: Compartmental model of TB transmission.

Based on presented information, we obtain the Ordinary Differential Equation System 6.1:

$$\begin{cases} \dot{S} = \Lambda - \alpha\lambda pSI - \alpha\lambda(1-p)SI - \mu_1 S \\ \dot{L_e} = \alpha\lambda pSI + \alpha\lambda rI(R_1 + R_2) + r_1 I + r_2 T + r_3 K - \widetilde{B} L_e \\ \dot{L_f} = hL_e - (\mu_1 + w + k_1 + k_2)L_f \\ \dot{I} = wL_f + qL_e - \widetilde{A} I + \alpha\lambda R_1 I + \alpha\lambda R_2 I + \alpha\lambda(1-p)SI \\ \dot{R_1} = g_1 L_e + k_1 L_f + \gamma I - \alpha\lambda r R_1 I - \mu_1 R_1 - \alpha\lambda R_1 I \\ \dot{R_2} = \sigma I + k_2 L_f + g_2 L_e - \alpha\lambda R_2 I - \alpha\lambda r R_2 I - \mu_1 R_2 \\ \dot{T} = \beta I - (\mu_1 + \mu_2 + r_2)T \\ \dot{K} = vI - (\mu_1 + \mu_2 + r_3)K \\ N = S + L_e + L_f + I + R_1 + R_2 + T + K \end{cases} \tag{6.1}$$

Where $\widetilde{A} = (r_1 + \gamma + \beta + \sigma + v + \mu_1 + \mu_2)$ and $\widetilde{B} = (\mu_1 + h + q + g_1 + g_2)$.

The dynamics of the disease at the level of all cities is managed by solving the system of differential equations to control the dynamics of the disease. This is the macroscopic level of the model. For individuals to move from city to city, they are managed by a model based on intelligent agents that manages each agent's behaviors, including the probability of deciding to travel and contamination during the trip. Once the individual arrives at his destination, he contributes to the evolution of the disease in the city. This is the microscopic level of the model. Note that at each simulation step, cities generate individuals with their status according to an estimated rate (see Tab. 6.3).

The probability of leaving city A to city B is calculated by $P(travel) = P(h_{AB})$ with A the source city and B the destination city. In this model, individual leaving his or her home city to a randomly chosen destination city must pass through a central point of the circle called a hub. The mobility agent model applied in this work is managed by an agent-based model.

C. Description of the ABM using ODD protocol

We develop a hybrid stochastic ABM in which TB dynamics among several cities is considered. To implement this ABM we used GAMA Platform [Grignard et al., 2013]. Several simulations are presented.

C.1. Overview

- *Purpose*: the purpose of the model is to assess the impact of population mobility on the spread of TB in a multi-scale environment.
- *Entities, state variables and scale*: (1) *Agent*: in this model we consider two types of agent. The first one is the individual. The second one is the city. Indeed, individual agent is located in a given agent city. Each individual agent has state variables as well as characteristics presented in Tab. 6.1. (2) *Spatial Units*: agent cities generate individual agents based on a generation rate. Individual agent can move from a city to others. State variables of cities are listed in Tab. 6.2.
- *Environment*: we assume that cities have the same population size in a virtual environment of size 50 X 50. The location of cities is a circle and is calculated by the function (6.2)

$$L = f\left(\frac{c_1}{2} + r_x cos\left(\frac{360}{b} * i\right), \frac{c_2}{2} + r_x sin\left(\frac{360}{b} * i\right)\right) \tag{6.2}$$

With $r_x = \left(\frac{c_1 - s*2}{2}\right)$ and i is the city number or identifier and s is the size of the city, c_1 is the length of the environment and c_2 the width of the environment, b is the number of cities and f represents a location function in a two-dimensional plane.

At each simulation time step, each city generates individual agents according to their states (susceptible, early latent, latent late, infectious, spontaneously recovered, recovered after treatment, transferred or lost to follow- up). The generation rate of this population is given by the variable z which is randomly selected between 0.001% and 1% closed interval.

- *Process overview and scheduling*: the model process is in discrete time steps representing 1 hour. At the beginning of the simulation, in cities, individual agents are in any state. The disease dynamics is managed by solving a differential equation system using RK4 method as applied in [Kasereka et al., 2014]. Individual agents have a probability of leaving a city to another. At each time step the sub-models are executed (movement, becoming infected, healing, updating of global variables, etc.).

Table 6.1: Description of agent state variables for the hybrid model

State variables	**Description**
Agent identifier	Unique agent id
Age	From 0 to 120
Sex	Male, Female
Susceptible?	Is the agent susceptible?
Early latent?	Is the agent early latent?
Latent late?	Is the agent latent late?
Sick?	Is the agent sick?
Spontaneously recovered?	Is the agent spontaneously recovered?
Recovery after treatment?	Is the agent recovery after treatment?
Transferred?	Is the agent transferred?
Lost to follow-up?	Is the agent lost to follow-up?
Sick days	Number of days the agent has been sick
Early latent days	Number of days the agent has been early latent
Latent late days	Number of days the agent has been latent late
Transferred days	Number of days the agent has been transferred
Lost to follow-up days	Number of days the agent has been Lost to follow-up
Spontaneously recovered days?	Number of days the agent has been spontaneously recovered?
Recovery after treatment days?	Number of days the agent has been recovery after treatment?
Location	Determines the location of the agent on the environment
In movement?	Is the agent in movement?
Neighbors	Represents the list of the agent's neighbors
Trip range of contact	Represents the radius of contamination of the agent during the trip. The default is taken between 1 and 5m.
Trip in contact with sick people?	Determine if the agent is in contact with sick people in it range during the trip.
Destination city	The city the agent is moving towards
Trip contact number	List of the number of contacts an agent has had during the trip
Trip average contacts	The average number of contacts an agent has had during the trip
Trip contact type	Random

C.2. Design concept

- *Basic principe*: the dynamics of TB is considered at two levels. (1) The first one is in the city (macroscopic). Here, the spread of the disease is based on mathematical model (Ordinary Differential Equation). 8 compartments are considered (susceptible, early latent, latent late, infectious,

Table 6.2: Description of city state variables

State variables	Description
City identifier	Unique city id
Total individual agent	The total number of agents in the city
Time generate agent	The total number of agents generated each time step

spontaneously recovered, recovered after treatment, transferred and lost to follow-up). The idea is that when a susceptible individual comes into contact with an infectious individual, it is possible that the susceptible individual may become exposed or infectious according to a rate of contact and a rate of transmission. People can travel from their cities to others. Destination are chosen randomly. (2) The second one is the individual (microscopic). Here, once individuals travel from their resident cities to another city, they are considered as agents. Indeed, during the trip, the dynamics of the disease is managed by an agent-based model.

- *Emergence*: the emergence of the system can be seen in the evolution of TB infection in all cities considered. In the macroscopic level, it depends on the contact rate and transmission rate between infectious people and susceptible people. In the microscopic level, it depends on the type of initially infectious agents, the other agents that come into contact with them along a radius of contamination, the duration of contact but also the frequency of contact.

- *Adaptation*: infectious agents can detect susceptible and cured agents. Once cured agents detect infectious agents, these agents avoid contact with them.

- *Interaction*: in this model we assume that agents within the same radius interact with each other and also with their environment. For example, if a susceptible agent is in a same radius with an infectious agent, it is possible that the susceptible agent become contaminated.

- *Stochasticity*: The movement of the agents with their specific states are stochastic. The choice of the destination city is random. Stochasticity is also in the TB contamination. During the traveling, if a susceptible agent comes into contact with an infectious agent, there is a certain probability that determines whether that agent becomes exposed or directly infectious. In addition, the length of time an agent remains in a state (susceptible, early latent, latent late, infectious, spontaneously recovered, recovered after treatment, transferred and lost to follow-up) is randomly chosen.

- *Observation*: data are collected at each execution of the model on individual agents according to their states (susceptible, early latent, latent late, infectious, spontaneously recovered, recovered after treatment, transferred and lost to follow-up). The output of the model is collected at each time step to observe the evolution of infectious agents over time.

C.3. Details

- *Initialization*: at the beginning of the simulation, a number of susceptible individuals is placed in all cities and only one city has in addition some infectious individuals.

- *Sub-model:*

- *Clock*: this sub-model manages time in the model. It is determined in hour, day, week, month and year. After every 24 hours, the hour variable is reset to zero and the day variable is incremented by 1. After every 7 days, the day variable is reset to zero and the week variable is incremented by 1. After every 4 weeks, the week variable is reset to zero and the month variable is incremented by 1. After every 12 months, the month variable is reset to zero and the year variable is incremented by 1. We therefore assume a month to 4 weeks (28 days).
- *Mobility*: agents move from one city to another. The choice of destination city is random. All information presented below are considering during the trip of agent from one city to another.
- *Contamination*: in the microscopic level, contamination is based on contact between a susceptible agent and an infectious agent, and the probability of TB transmission. If a susceptible agent is infected then he will change his status from susceptible to exposed (Early latent (Le) / Latent late (Lf)) or infectious. In the macroscopic level, contamination is managed by the resolution of the differential equation using RK4 method.
- *Early latent*: An exposed agent (L_e) progresses to (L_f) or to infectious according to a certain probability of progression. The time that the agent will remain in the state L_e before moving to L_f is determined by a certain probability as well.
- *Latent late*: an exposed agent (L_f) progresses to infectious according to a certain probability of progression. The length of time the agent will remain in the (L_f) state before becoming infectious is also determined by a certain probability.
- *Recover:* infectious agents recover based on a probability of spontaneous recovery or a probability of recovery after taking medication.
- *Relapse:* cured agents may relapse and become exposed or infectious based on a certain probability.
- *Lost to follow-up:* when an infectious agent stops taking medication before the end of treatment, it is considered lost to follow-up. Infectious agents become lost to follow-up with a certain probability.
- *Global variables update:* all global variables are updated at the end of each time step. At the same time also the number and percentage of susceptible, exposed (Early latent and Latent late), infected, transferred, lost to follow-up, Recovered (spontaneously and after treatment) agents are all calculated.

D. Simulations of the model

Tab. 6.3 presents the baseline parameter values for simulations as well as their meanings. Most of them were taken from the literature and other were based on data at our disposal.

To simulate this model we use the same parameters presented in Tab. 6.3 that describe values of each parameter and references from the literature. To simulate this model we will consider the following case: First, we consider 6 cities and a high mobility of people between those cities. Second, we simulate the model by varying the mobility rate of individuals (low mobility rate for infected and infectious individuals) between the 6 cities.

This model is implemented using the GAMA platform [Grignard et al., 2013] which is a platform designed for field experts, modelers and computer scientists. It is therefore a complete modeling and

Table 6.3: Parameter values for the metapopulation model

Prms	Meaning	Value	Reference	Estimated
Λ	Rate of recruitment ($\Lambda \times N$)	0.0100		Yes
μ_1	Natural death rate	0.0222	[Ozcaglar et al., 2012]	
μ_2	Mortality rate linked to TB	0.040	[Bisuta et al., 2018]	
γ	Recovered rate after treatment (I to R_1)	0.840	[Bisuta et al., 2018]	
σ	Spontaneously recovered rate (I to R_2)	0.250	[Passion-Santé, 2015]	
α	Contact rate	0.0010		Yes
λ	Rate of transmission	0.100	[Adebiyi, 2016]	
$1-p$	Fraction of fast-developing active TB	0.05	[Blower et al., 1995, Zhao et al., 2017]	
β	Rate of transfer to a hospital	0.010		Yes
v	Rate of lost to follow-up	0.030	[Bisuta et al., 2018]	
q	Progression rate (L_e to I)	0.129	[Trauer et al., 2014]	
h	Rate of progression of TB (L_e to L_f)	0.821	[Trauer et al., 2014]	
r	Reinfection rate (R_i to L_e) with i=1,2	0.030	[Blower et al., 1995]	
r_1	Rate of re-infection (I to L_e)	0.63	[Trauer et al., 2014]	
r_2	Rate of re-infection (T to L_e)	0.63	[Trauer et al., 2014]	
r_3	Rate of re-infection (K to L_e)	0.63	[Trauer et al., 2014]	
g_1	Rate of recovered (L_e to R_1)	0.840	[Bisuta et al., 2018]	
g_2	Rate of spontaneously recovered (L_e to R_2)	0.250	[Passion-Santé, 2015]	
k_1	Rate of recovered (L_f to R_1)	0.840	[Bisuta et al., 2018]	
k_2	Rate of spontaneously recovered (L_f to R_2)	0.250	[Passion-Santé, 2015]	
w	Rate of progression (L_f to I)	0.075	[Trauer et al., 2014]	
m	Mobility rate	0.00001 - 0.01		Yes
gen^*	Individual generation rate in city	0.00001 - 0.01		Yes

simulation development environment for the construction of spatially explicit multi-agent simulations. This platform was designed completely in Java. As a free tool, GAMA uses the GAML (GAma Modeling Language) language for coding [Grignard et al., 2013].

For all simulations, we consider that the disease exists in one of the cities at the beginning of the simulation. This allows us to evaluate the impact of population mobility on the disease dynamics (TB).

Simulation with a high mobility rate for all individuals.

By simulating the proposed model with the basic parameters shown in Tab. 6.3. We consider the dynamics of TB which spreads globally over 6 connected cities with the mobility rate of all individual ($S, L_e, L_f, I, T, K, R_1$ and R_2) equal to 0.01. Fig. 6.3 shows the evolution of the model during simulation.

The results obtained are shown in Fig. 6.4 for all the cities (global) and in Fig. 6.5 for each city separately (one by one city):

Simulation with basic parameters and consideration of a low mobility rate for I, L_e and L_f individuals

The environment with 6 cities connected via a hub is presented in Fig. 6.6. The mobility rate considered for I, L_e and L_f is equal to 0.00001.

The results obtained are shown in Fig. 6.7 for all the cities and in Fig. 6.8 for each city separately.

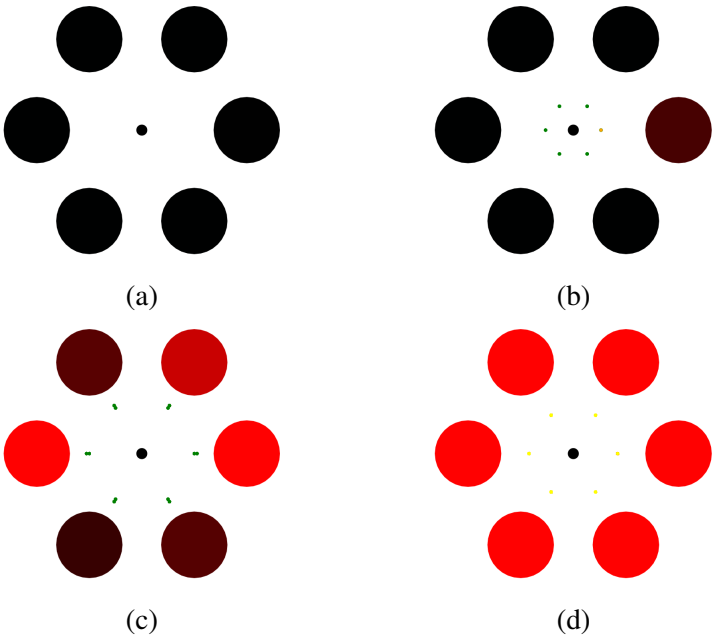


Figure 6.3: Presentation of the virtual environment with 6 cities (circles) interconnected via a hub. (a) simulation at time $t = 0$, (b) simulation at time $t = 79$, (c) simulation at time $t = 262$, (d) simulation at time $t = 328$. The concentration of the red color of the city is proportional to the level of infectivity of the city.

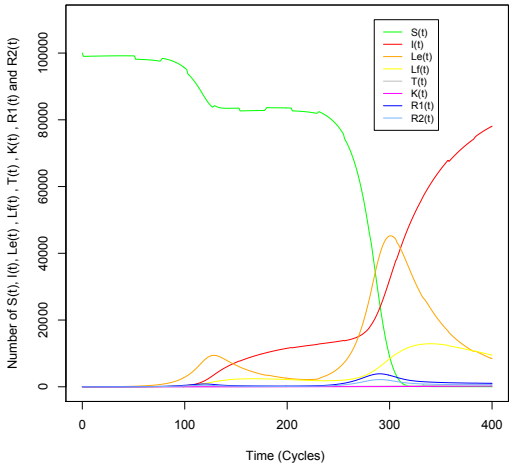


Figure 6.4: Evolution of the model for all cities considered globally

E. Discussion of the results

The hybrid metapopulation model implemented and simulated shows that individual mobility has an impact on the spread of tuberculosis in the population. Indeed, Figs. 6.4 and 6.5 illustrate that when there is a large number of people moving from city to city (mobility rate equal to 0.01 of the population according to its status), the disease spreads to all cities. This is justified by the fact that infected persons moving from their home city to another city contribute to the epidemiology of the destination city (randomly selected). The persistence of tuberculosis in poor countries can be partially justified by the rural migration.

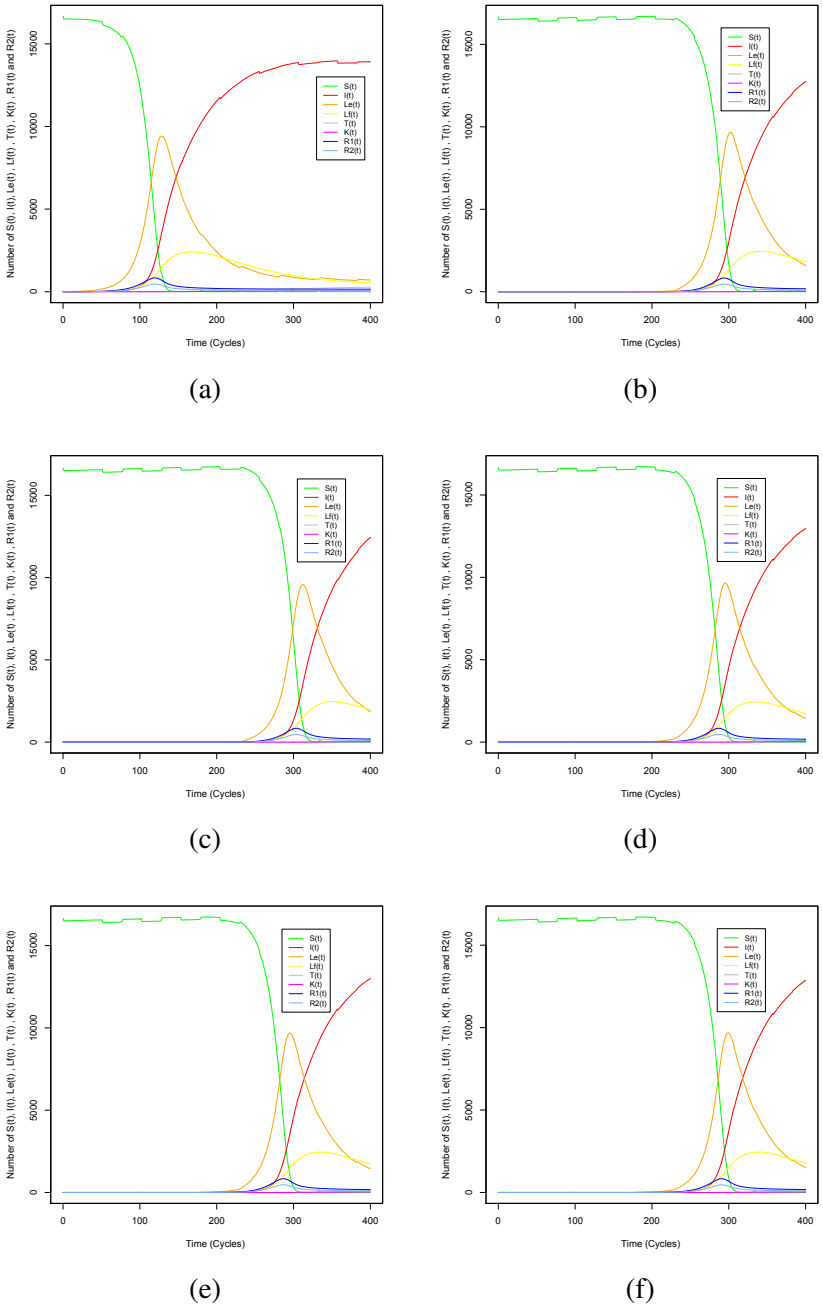


Figure 6.5: Evolution of the model on a virtual environment with 6 cities (circles) interconnected via a hub. (a) city 1, (b) city 2, (c) city 3, (d) city 4, (e) city 5 and (f) city 6.

For example, in Democratic Republic of the Congo, poor people living in the provinces move to the capital (Kinshasa) to seek a better life. Kinshasa being already one of the cities most affected by TB [Bisuta et al., 2018], the arrival of new cases from other cities is one of the factors contributing to the persistence of tuberculosis in this city.

By reducing the mobility rate to 0.00001 for people with TB infection and people with latent TB, simulations show that the disease does not spread in all cities as shown in figs. 6.7 and 6.8. This means that restricting the mobility (between cities) of infectious and latent people is one of the measures to be taken to control the spread of tuberculosis across a country.

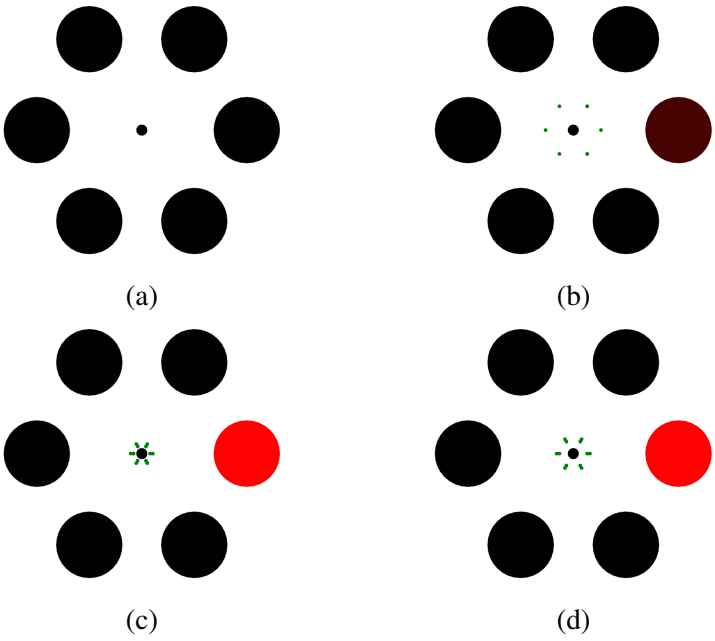


Figure 6.6: virtual environment with 6 cities (circles) interconnected via a hub. (a) simulation at time $t = 0$, (b) simulation at time $t = 79$, (c) simulation at time $t = 262$, (d) simulation at time $t = 328$. The concentration of the red color of the city is proportional to the level of infectivity of the city.

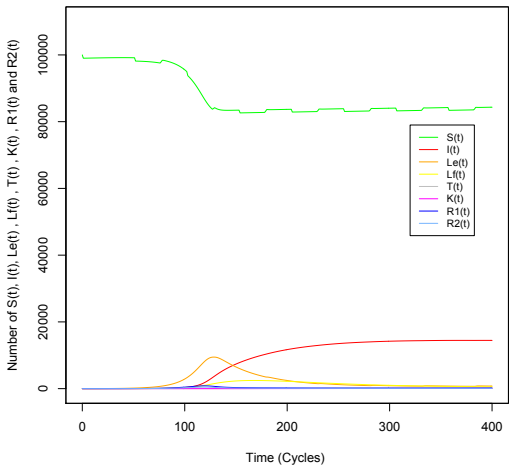


Figure 6.7: Evolution of the model for all cities considered globally

Improving the living conditions of the population in the provinces and decentralizing TB care centers can be a palliative solution to the rural migration. With this strategy, people can simply stay in their home cities because the living and care conditions are the same as in other cities.

The model preseted here deal with tuberculosis spread over several cities and simulated it on a virtual environment composed of several cities placed on a circle and having a central point as a mandatory passage for the choice of the destination city for travellers. The disease dynamics at the level of each city was represented by an 8-compartment model that manages the spread of TB by solving an ordinary differential equation. To ensure the mobility of people from city to city, individuals and cities have been

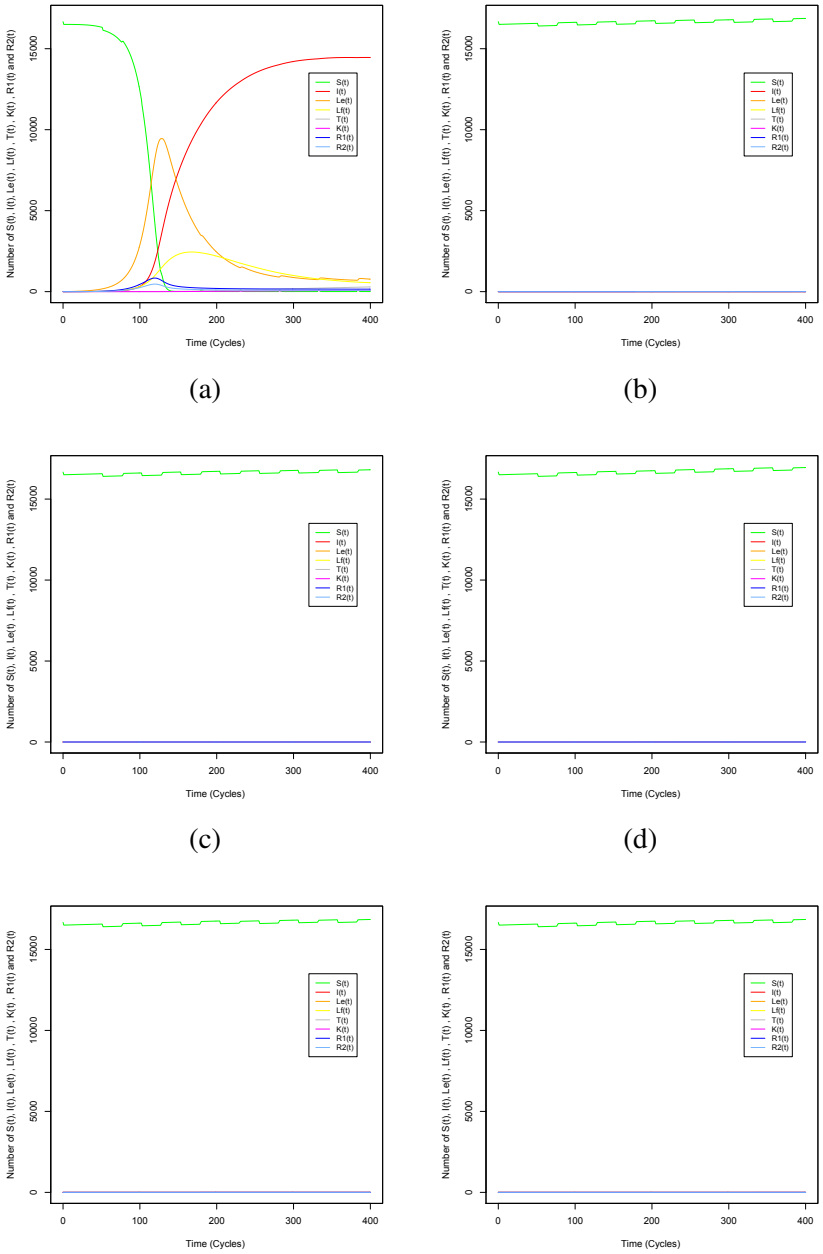


Figure 6.8: Evolution of the model on a virtual environment with 6 cities (circles) interconnected via a hub. (a) city 1, (b) city 2, (c) city 3, (d) city 4, (e) city 5 and (f) city 6.

considered as intelligent agents. At each time step, cities generated individuals who had to travel from one city to another randomly selected according to a mobility rate. The implemented model is called hybrid because it couples the differential equations applied in each city to the intelligent agents that act on the individual by considering his heterogeneous behaviors such as mobility, random choice of destination (decision making), change of status (interaction with other agents), etc. This model benefits from the advantages of these two modeling-simulation approaches for complex systems. The model implemented here has the advantage of not requiring a large number of parameters and a high capacity in terms of machine power. In addition to the advantage of being synthetic, this hybrid model benefits from the

analytical character of mathematical models. Agent-based modeling enriches this model by imposing a stochastic character on it through random facts introduced into the random choice of the destination city for individuals but also into the generation of individuals in different cities at a randomly chosen rate.

The consideration of the individual as an entity in its own right and the management of his or her behaviour gives the microscopic aspect to the model set up and brings it as close as possible to reality. The mathematical management of the spread of the disease in cities gives a macroscopic aspect to the model. This model therefore draws its richness from this dynamic at two different scales, which gives the emergence of the model at the global level. As a result, it seems obvious that the coupling of mathematical models to agent-based models will be applied when the dynamics of the complex system under consideration is at different scales. The implemented hybrid model does not require enough computing power compared to the general agent-based model which requires high performance simulation hardware.

The results obtained affirm that the mobility of individuals from city to city has a significant impact on the spread of tuberculosis in the population. Controlling the rate of population mobility from a city to another is one of the most important measures for large-scale disease control.

As part of the prospects, we intend to integrate vaccination at the microscopic level of this model. This should make it possible to see its impact at the global level of the model.

6.3 Conclusion

This chapter presented the coupling of a compartmental model based on differential equations from mathematics and an agent-based model from artificial intelligence. The chapter first presents notions on model coupling by defining usual terms, showing the advantages and difficulties of coupling before presenting the types of coupling. A case study of modeling and simulation of TB propagation in DRC on a multi-scale environment concludes this chapter.

This model is very interesting for several reasons. The model can easily incorporate any mathematical model for the dynamics of any infectious disease within interconnected cities. Unlike a classical metapopulation model, the model proposed here takes into account the contamination of individuals during the journey from one city to another. MODEL 4 differs from other models presented in this thesis because it manages the dynamics of disease at different levels. In contrast to traditional agent-based and mathematical modeling, this new approach of hybrid modeling of epidemiological phenomena allows to understand the spread of infectious diseases at different levels/scales.

The modeling approach coupling mathematics to multi-agent systems offers many opportunities for modelers to manipulate all facets of the problem to be solved. Mathematics will enable the description, understanding and prediction of the evolution of the system in exercise thanks to its analytical and synthetic characteristics. Multi-agent systems will give the modeler the power to manipulate the individuals in the system as entities in their own right capable of autonomous actions but also of interacting with other entities in an environment. The model, called hybrid, because it is the result of a coupling of models, and is able to manage the dynamics of the complex system at different scales without any problem.

The proposed hybrid model provides a further understanding of the spread of TB than a classical agent-based model, in the sense that the hybrid model allows to calibrate and to measure the actions that need to be taken at the individual or village level (microscopic level) to reduce the incidence/prevalence of TB at the global level, i.e. at the level of the whole country (macroscopic level).

Chapter 7

General conclusion and future works

The last chapter is devoted to the general conclusion of this dissertation. It presents the general discussion and some of the work we plan to carry out in the future.

7.1 General discussion

This thesis focuses on modeling and simulation of complex systems by using differential equations and intelligent agents in a single model and application of the resulting model on tuberculosis in a developing country, the Democratic Republic of the Congo. We began by understanding the biology and epidemiology of tuberculosis. This gave us a general overview of the disease worldwide and more specifically in DRC. A statistical study of available data was also carried out and results obtained show that the TB situation in DRC remains endemic and therefore measures must be put in place in order to develop control mechanisms in the country.

A literature review on modeling and simulation of infectious disease spread was also presented. Some TB models were presented and criticized after successively introducing mathematical modeling based on differential equations and agent-based modeling derived from artificial intelligence. We were especially interested in comparing these two approaches to solve the same problem and to see to what extent they can be applied in the same single model called "hybrid stochastic". Indeed, we initially studied mathematical modeling and then agent-based modeling of the spread of infectious diseases in population. This allowed us to identify the strengths and weaknesses of each approach. Concrete cases of application of these approaches have been carried out on the spread of tuberculosis using DRC data.

Four models (MODEL 1, MODEL 2, MODEL 3 and MODEL 4) were proposed and implemented :

1. The first was based on differential equations. The concern here was to model, simulate and analyze a mathematical model of the spread of tuberculosis in a population. An 8-compartment mathematical model based on the natural history of TB has been developed. The particularity of this model was to take into account the groups of individuals which are generally neglected in modeling the spread of diseases, such as transferred, lost to follow-up, early and late latent groups. A basic mathematical analysis was performed, the basic reproduction rate $\mathcal{R}_0$ was obtained and used to control the evolution of the disease in the population. The stability of the equilibrium points has been demonstrated through numerical simulations. They have demonstrated that with certain

parameters, TB can be totally eliminated in DRC. For this reason, the Congolese health system must take into account all the axes of intervention and focus on the treatment of people with latent TB, because latents/exposed persons with rapid progression are responsible for the increase in incidence in the short and medium term. On the other hand, the exposure to slow progression will be responsible for the persistent incidence in the long term and the maintenance of the disease and delay the elimination.

2. The second mathematical model was also based on differential equations and dealt with susceptible and multi-resistant tuberculosis in the Congolese population. Here, a double-stranded compartmental model (SEIR for each strand and representing susceptible or multi-resistant TB) was proposed. A basic mathematical analysis of this model was carried out. The baseline reproduction rates for susceptible and resistant TB have been found and have shown that the TB situation in DRC is still endemic and that a person with resistant TB infects 4 times more people than a person with susceptible TB. Simulations carried out have shown that the elimination of this disease in DRC is possible, but the Congolese health system must monitor contacts with people infected, especially with multi-resistant TB, to significantly reduce contamination. The model also showed, as the first one, that the treatment of latents is a life-saving measure to hopefully eliminate TB in DRC.

3. The third model was based on intelligent agents derived from multi-agent systems, a branch of artificial intelligence. Here we have modelled the spread of tuberculosis by considering that individuals are agents, these agents can interact with each other and, they can act and move on an environment. Two population structures were proposed. We first consider a population mixed on a grid environment on which agents are positioned in cells. These agents can move from one cell to another and therefore interact with other agents. This model uses the first mathematical model to distinguish groups of people according to their states, but the transfer of people from one group to another is supported by probabilities. The second population structure proposed is a 4-level one. Level 1 corresponds to the household where individual contacts are very close, level 2 is direct neighbour where individual contacts are close, level 3 is neighbourhood where individual contacts are causal, and finally the level 4 is the community with a random network of contact. Through these models, agent-based modeling has shown its efficiency and finesse. Indeed, it has allowed us to consider individuals as entities in their own right and to manage them by associating to each of them an algorithm that leads them to reach a given goal.

4. The fourth and last model shows a possible implementation of the mathematical approach coupled with the agent approach. This model, called hybrid, allows several levels of abstraction of the model to be considered. With this model, it is possible to take into account an individual or a group of individuals as needed. The consideration of the heterogeneous behaviours of individuals and the exploitation of the analytical and synthetic aspect of mathematics in the resolution of dynamic systems is the strength of this model. This model has been applied to the spread of TB between several interconnected cities and has shown the impact of population mobility from city to city on the dynamics of the disease. Thanks to this model, public health authorities of DRC will be able to assess the question: "*What actions need to be conducted at the local level to reduce the incidence of the disease at the global level despite the mobility of individuals*?".

Based on research presented in this thesis, it is clear that the choice of a modeling approach is an important task for a modeler. If the need is to have results in the form of means or proportions and the impact of individual behaviours on the spread of the disease is not the subject of the study, the mathematical approach is more appropriate to this problem. On the other hand, if the expected result depends on the heterogeneous behaviour of individuals, agent-based modeling approach is the most appropriate. The hybrid model coupling mathematics and intelligent agents will be interesting when the overall result of the problem depends on several scales. It will then be up to the modeler to define a compromise between the models resulting from the different approaches because the levels of abstraction may not be the same.

7.2 Future works

With the epidemiological data on the DRC at our disposal, we intend to integrate the standard of living (poverty) of the Congolese population into the study of tuberculosis dynamics. This should allow us to measure the relationship between the spread of the disease and the population's standard of living by province. The integration of cognition, especially the notion of rationality in the modeling of the spread of this disease is among the work we intend to do.

Appendix 1

.1 Supplementary materials

The concrete realization of this thesis required the use of several tools and programming languages. This section presents web links to the source codes we developed (GAMA PLATFORM using Gaml language, PYTHON and R) and statistics on data provided by PNLT of DRC.

.1.1 MODEL 1

The source codes (GAML and R) and results obtained are available online **HERE**

.1.2 MODEL 2

The source codes (GAML and R) and results obtained are available online **HERE**

.1.3 MODEL 3

The source codes (GAML and R) and results obtained are available online **HERE**

.1.4 MODEL 4

The source codes (GAML and R) and results obtained are available online **HERE**

To run these source codes, download GAMAPLATFORM 1.8 url: `https://gama-platform.github.io/download` for free. Please be sure that you have JDK or JRE installed in your system. Create a new model and copy/paste the model to your GAMA, file: *.gaml. The R files help to have friendly plots.

.1.5 Statistics on TB data from DRC

The source codes (PYTHON) and results obtained are available online **HERE**. To run our source codes, please use Jupyter Notebook.

Bibliography

[Abu-Raddad et al., 2009] Abu-Raddad, L. J., Sabatelli, L., Achterberg, J. T., Sugimoto, J. D., Longini, I. M., Dye, C., and Halloran, M. E. (2009). Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics. *Proceedings of the National Academy of Sciences*, 106(33):13980–13985.

[Adebiyi, 2016] Adebiyi, A. O. (2016). Mathematical modeling of the population dynamics of tuberculosis. Master's thesis, University of the Western Cape.

[Ait-Khaled et al., 1999] Ait-Khaled, N., Enarson, D. A., Initiative, S. T., et al. (1999). Tuberculose: manuel pour les étudiants en médecine. Technical report, Gen'eve : Organisation mondiale de la Santé.

[Anderson and May, 1992] Anderson, R. M. and May, R. M. (1992). *Infectious diseases of humans: dynamics and control*. Oxford university press.

[Apollinaire et al., 2016] Apollinaire, N. M., Rebecca, W. O., and Yengo Vala-ki sisa, M. (2016). Optimal control of a model of gambiense sleeping sickness in humans and cattle. *American Journal of Applied Mathematics*, 4(5):204–216.

[Arnaud, 1991] Arnaud, A.-J. (1991). Jean-louis le moigne, la modélisation des systèmes complexes, 1990. *Droit et Société*, 19(1):424–424.

[Atangana et al., 2014] Atangana, A., Goufo, D., and Franc, E. (2014). Computational analysis of the model describing hiv infection of cd4. *BioMed research international*, 2014:1–7.

[Auchincloss and Garcia, 2015] Auchincloss, A. H. and Garcia, L. M. T. (2015). Brief introductory guide to agent-based modeling and an illustration from urban health research. *Cadernos de saude publica*, 31:65–78.

[Axelrod, 1997] Axelrod, R. (1997). *The complexity of cooperation: Agent-based models of competition and collaboration*, volume 3. Princeton University Press.

[Bentout,] Bentout, S. *Mathématiques Appliquées à Quelques modèles épidémiologiques.* PhD thesis.

[Bisuta et al., 2018] Bisuta, S. F., Kayembe, P. K., Kabedi, M.-J. B., Situakibanza, H. N., Ditekemena, J. D., Bakebe, A. M., Lay, G. O., Mesia, G. K., Kayembe, J.-M. N., and Fueza, S. B. (2018). Trends of bacteriologically confirmed pulmonary tuberculosis and treatment outcomes in democratic republic of the congo: 2007-2017. *Ann. Afr. Med*, 11(4):e2974–e2985.

[Bisuta Fueza et al., 2006] Bisuta Fueza, S., Kashongwe, M., Kayembe, N. M., Mbaki, N., R, B., JP, S. K., Muyembe, T., and Bakaswa, N. G. (2006). Prise en charge de la tuberculose à bacilles multirésistants avec les antituberculeux de seconde ligne à kinshasa : résultats préliminaires. *Congo Médical*, 4(6):504–512.

[Bisuta-Fueza1 et al., 2019] Bisuta-Fueza1, S., Kayembe-Ntumba1, J. M., Kabedi-Bajani, M.-J., Sabwe, P. M., Tuma, H. S.-N., Simelo, J.-P., Sumaili-Kiswaya, E., Ditekemena-Dinanga, J., and Kayembe-Kalambayi, P. (2019). Multidrug-resistant tuberculosis in the democratic republic of congo: Analysis of continuous surveillance data from 2007 to 2016. *Journal of Tuberculosis Research*, 7(1):25–44.

[Blower et al., 1998] Blower, S., Porco, T., and Lietman, T. (1998). Tuberculosis: the evolution of antibiotic resistance and the design of epidemic control strategies. *Mathematical models in medical and health sciences*, page 1.

[Blower et al., 1996a] Blower, S., Small, P., and Hopewell, P. (1996a). Control strategies for tuberculosis epidemics: new models for old problems. *Science*, 273(5274):497–500.

[Blower and Chou, 2004] Blower, S. M. and Chou, T. (2004). Modeling the emergence of the'hot zones': tuberculosis and the amplification dynamics of drug resistance. *Nature medicine*, 10(10):1111.

[Blower and Gerberding, 1998] Blower, S. M. and Gerberding, J. L. (1998). Understanding, predicting and controlling the emergence of drug-resistant tuberculosis: a theoretical framework. *Journal of molecular medicine*, 76(9):624–636.

[Blower et al., 1995] Blower, S. M., Mclean, A. R., Porco, T. C., Small, P. M., Hopewell, P. C., Sanchez, M. A., and Moss, A. R. (1995). The intrinsic transmission dynamics of tuberculosis epidemics. *Nature medicine*, 1(8):815.

[Blower et al., 1996b] Blower, S. M., Small, P. M., and Hopewell, P. C. (1996b). Control strategies for tuberculosis epidemics: New models for old problems. *Science*, 273(5274):497–500.

[Caminero et al., 2013] Caminero, J., Van Deun, A., Fujiwara, P., et al. (2013). Guidelines for clinical and operational management of drug-resistant tuberculosis. *Paris, France: International Union Against Tuberculosis and Lung Disease*, pages 18–19.

[Capera et al., 2003] Capera, D., Georgé, J.-P., Gleizes, M.-P., and Glize, P. (2003). The amas theory for complex problem solving based on self-organizing cooperative agents. In *WET ICE 2003. Proceedings. Twelfth IEEE International Workshops on Enabling Technologies: Infrastructure for Collaborative Enterprises, 2003.*, pages 383–388. IEEE.

[Carlos-Chavez et al., 2001] Carlos-Chavez, C., Zhilan, F., and Huang, W. (2001). On the computation of and its role on global stability. *Institute for Mathematics and its Application*, 125.

[Castillo-Chavez and Feng, 1997] Castillo-Chavez, C. and Feng, Z. (1997). To treat or not to treat: the case of tuberculosis. *Journal of mathematical biology*, 35(6):629–656.

[Castillo-Chavez and Song, 2004] Castillo-Chavez, C. and Song, B. (2004). Dynamical models of tuberculosis and their applications. *Mathematical biosciences and engineering*, 1(2):361–404.

[Chaib-draa, 1997] Chaib-draa, B. (1997). Connection between micro and macro aspects of agent modeling. In *Proceedings of the first international conference on Autonomous agents*, pages 262–267. ACM.

[Chowell et al., 2016] Chowell, G., Sattenspiel, L., Bansal, S., and Viboud, C. (2016). Mathematical models to characterize early epidemic growth: A review. *Physics of life reviews*, 18:66–97.

[Cisse et al., 2007] Cisse, C., Gazhi, Y., Thure-badiane, N., Wotto-Gaye, G., Moreau, J., and Hanne, A. (2007). Tuberculose et grossesse: épidémiologie et pronostic au chu de dakar. *La Lettre du gynécologue*, 325:8–10.

[Coquillard et al., 1997] Coquillard, P., Hill, D. R., and Sime-Ngando, T. (1997). *Modélisation et simulation d'écosystèmes: des modèles déterministes aux simulations à évènements discrets*. Masson Paris.

[De Espíndola et al., 2011] De Espíndola, A. L., Bauch, C. T., Cabella, B. C. T., and Martinez, A. S. (2011). An agent-based computational model of the spread of tuberculosis. *Journal of Statistical Mechanics: Theory and Experiment*, 2011(05):P05003.

[Departement, 2017] Departement, G. L. I.-S. (2017). *Model tuberculosis diagnostic algorithms*. World Health Organization.

[Diekmann and Heesterbeek, 2000] Diekmann, O. and Heesterbeek, J. A. P. (2000). *Mathematical epidemiology of infectious diseases: model building, analysis and interpretation*, volume 5. John Wiley & Sons.

[Djomegni et al., 2017] Djomegni, P. T., Govinder, K., and Goufo, E. D. (2017). Movement, competition and pattern formation in a two prey–one predator food chain model. *Computational and Applied Mathematics*, pages 1–15.

[Dori and Sillitto, 2017] Dori, D. and Sillitto, H. (2017). What is a system? an ontological framework. *Systems Engineering*, 20(3):207–219.

[Dowdy et al., 2013] Dowdy, D. W., Dye, C., and Cohen, T. (2013). Data needs for evidence-based decisions: a tuberculosis modeler's 'wish list'. *The International Journal of Tuberculosis and Lung Disease*, 17(7):866–877.

[Drogoul, 1993] Drogoul, A. (1993). *De la simulation multi-agents à la résolution collective de problèmes*. PhD thesis, Thesis at University of Paris IV.

[Drogoul and Gaudou, 2013] Drogoul, A. and Gaudou, B. (2013). Methods for agent-based computer modelling.

[Duboz, 2004] Duboz, R. (2004). Intégration de modeles hétérogenes pour la modélisation et la simulation de systemes complexes. *Application à la modélisation multiéchelles en écologie marine*.

[Duperret, 2016] Duperret, J.-C. (2016). De la modélisation du monde au monde des modèles (2).

[Dye, 2008] Dye, C. (2008). Breaking a law: tuberculosis disobeys styblo's rule.

[End TB Group, 2018] End TB Group, W. H. O. (2018). Bedaquiline- and delamanid containing regimens achieve excellent interim treatment response without safety concerns:endtb interim analysis. Technical report, World Health Organization.

[Epstein, 2009] Epstein, J. M. (2009). Modelling to contain pandemics. *Nature*, 460(7256):687.

[Falzon et al., 2017] Falzon, D., Schünemann, H. J., Harausz, E., González-Angulo, L., Lienhardt, C., Jaramillo, E., and Weyer, K. (2017). World health organization treatment guidelines for drug-resistant tuberculosis, 2016 update. *European Respiratory Journal*, 49(3):1602308.

[Feng and Castillo-Chavez, 1998] Feng, Z. and Castillo-Chavez, C. (1998). Mathematical models for the disease dynamics of tubeculosis.

[Feng et al., 2000] Feng, Z., Castillo-Chavez, C., and Capurro, A. F. (2000). A model for tuberculosis with exogenous reinfection. *Theoretical population biology*, 57(3):235–247.

[Feng et al., 2001] Feng, Z., Huang, W., and Castillo-Chavez, C. (2001). On the role of variable latent periods in mathematical models for tuberculosis. *Journal of dynamics and differential equations*, 13(2):425–452.

[Ferber and Weiss, 1999] Ferber, J. and Weiss, G. (1999). *Multi-agent systems: an introduction to distributed artificial intelligence*, volume 1. Addison-Wesley Reading.

[Fianyo, 2001] Fianyo, Y. E. (2001). *Couplage de modèles à l'aide d'agents: le système OSIRIS*. PhD thesis, ANRT [diff.].

[Fishwick, 1997] Fishwick, P. A. (1997). Computer simulation: growth through extension. *Transactions of the Society for Computer Simulation*, 14(1):13–24.

[Fishwick and Zeigler, 1992] Fishwick, P. A. and Zeigler, B. P. (1992). A multimodel methodology for qualitative model engineering. *ACM Transactions on Modeling and Computer Simulation (TOMACS)*, 2(1):52–81.

[Gaudou, 2016] Gaudou, B. (2016). *Toward complex models of complex systems*. PhD thesis, University Pierre et Marie Curie.

[Goufo et al., 2014] Goufo, E. F. D., Maritz, R., and Munganga, J. (2014). Some properties of the kermack-mckendrick epidemic model with fractional derivative and nonlinear incidence. *Advances in Difference Equations*, 2014(1):278.

[Goufo et al., 2017] Goufo, E. F. D., Maritz, R., and Pene, M. K. (2017). A mathematical and ecological analysis of the effects of petroleum oil droplets breaking up and spreading in aquatic environments. *International Journal of Environment and Pollution*, 61(1):64–71.

[Goufo et al., 2016] Goufo, E. F. D., Pene, M. K., and Mugisha, S. (2016). Stability analysis of epidemic models of ebola hemorrhagic fever with non-linear transmission. *Journal of Nonlinear Sciences & Applications (JNSA)*, 9(6):4191–4205.

[Grignard et al., 2013] Grignard, A., Taillandier, P., Gaudou, B., Vo, D. A., Huynh, N. Q., and Drogoul, A. (2013). Gama 1.6: Advancing the art of complex agent-based modeling and simulation. In *International conference on principles and practice of multi-agent systems*, pages 117–131. Springer.

[Grimm et al., 2006] Grimm, V., Berger, U., Bastiansen, F., Eliassen, S., Ginot, V., Giske, J., Goss-Custard, J., Grand, T., Heinz, S. K., Huse, G., et al. (2006). A standard protocol for describing individual-based and agent-based models. *Ecological modelling*, 198(1-2):115–126.

[Grimm et al., 2010] Grimm, V., Berger, U., DeAngelis, D. L., Polhill, J. G., Giske, J., and Railsback, S. F. (2010). The odd protocol: a review and first update. *Ecological modelling*, 221(23):2760–2768.

[Guégan and Choisy, 2008] Guégan, J.-F. and Choisy, M. (2008). *Introduction à l'épidémiologie intégrative*. De Boeck Supérieur.

[Hanski et al., 1997] Hanski, I., Gilpin, M. E., and McCauley, D. E. (1997). *Metapopulation biology*, volume 454. Elsevier.

[Hassoumi, 2015] Hassoumi, I. (2015). *Approche multi-agents de couplage de modèles pour la modélisation des systèmes complexes spatiaux: application à l'aménagement urbain de la ville de Métouia*. PhD thesis, Paris 6.

[Helper et al., 2002] Helper, S., Pil, F., Sako, M., Takeishi, A., Warburton, M., and MacDuffie, J. P. (2002). Modularization and outsourcing: Implications for the future of automotive assembly" management of the extended enterprise" research team.

[Hickson et al., 2012] Hickson, R. I., Mercer, G. N., and Lokuge, K. M. (2012). A metapopulation model of tuberculosis transmission with a case study from high to low burden areas. *PloS one*, 7(4):e34411.

[Institut National de la Statistique, 2017] Institut National de la Statistique, K. (2017). Annuaire satistique 2015. Technical report, ‚Ministère du Plan/RDC.

[Iskandar et al., 2017] Iskandar, T., Chaniago, N. A., Munzir, S., Halfiani, V., and Ramli, M. (2017). Mathematical model of tuberculosis epidemic with recovery time delay. In *AIP Conference Proceedings*, volume 1913, page 020021. AIP Publishing.

[Kalton et al., 2016] Kalton, A., Falconer, E., Docherty, J., Alevras, D., Brann, D., and Johnson, K. (2016). Multi-agent-based simulation of a complex ecosystem of mental health care. *Journal of medical systems*, 40(2):39.

[Kant, 2012] Kant, J.-D. (2012). Apports des mathématiques et de l'informatique pour la modélisation en sciences humaines et sociales. *Mathématiques et sciences humaines. Mathematics and social sciences*, (197):47–64.

[Karafyllidis and Thanailakis, 1997] Karafyllidis, I. and Thanailakis, A. (1997). A model for predicting forest fire spreading using cellular automata. *Ecological Modelling*, 99:87–97.

[Kasaie et al., 2014] Kasaie, P., Andrews, J. R., Kelton, W. D., and Dowdy, D. W. (2014). Timing of tuberculosis transmission and the impact of household contact tracing. an agent-based simulation model. *American journal of respiratory and critical care medicine*, 189(7):845–852.

[Kasaie et al., 2013] Kasaie, P., Dowdy, D. W., and Kelton, W. D. (2013). An agent-based simulation of a tuberculosis epidemic: understanding the timing of transmission. In *Proceedings of the 2013 Winter Simulation Conference: Simulation: Making Decisions in a Complex World*, pages 2227–2238. IEEE Press.

[Kasereka, 2014] Kasereka, S. (2014). Approche hybride de la modélisation des épidémies et estimation des paramètres. Master's thesis, Vietnam National University - IFI, Hanoi, Vietnam.

[Kasereka et al., 2019] Kasereka, S., Goufo, E.-F. D., Vinh, H. T., Ndondo, A., and Bisuta, S. (2019). Analysis and simulation of a mathematical model of pulmonary tuberculosis transmission, case study of dr. congo. *In press (2019)*.

[Kasereka et al., 2014] Kasereka, S., Kasoro, N., and Chokki, A. P. (2014). A hybrid model for modeling the spread of epidemics: Theory and simulation. In *ISKO-Maghreb: Concepts and Tools for knowledge Management (ISKO-Maghreb), 2014 4th International Symposium*, pages 1–7. IEEE.

[Kasereka et al., 2018a] Kasereka, S., Kasoro, N., Kyamakya, K., Goufo, E.-F. D., Chokki, A. P., and Yengo, M. V. (2018a). Agent-based modelling and simulation for evacuation of people from a building in case of fire. *Procedia Computer Science*, 130:10–17.

[Kasereka et al., 2018b] Kasereka, S., Le Strat, Y., and Léon, L. (2018b). Estimation of infection force of hepatitis c virus among drug users in france. In *Recent Advances in Nonlinear Dynamics and Synchronization*, pages 319–344. Springer.

[Keeling and Rohani, 2011] Keeling, M. J. and Rohani, P. (2011). *Modeling infectious diseases in humans and animals*. Princeton University Press.

[Landy and Vinh, 2013] Landy, R. H. and Vinh, H. T. (2013). A multi-agent model to simulate the spread of contagious diseases in urban areas. In *2013 International Conference on Soft Computing and Pattern Recognition (SoCPaR)*, pages 276–281. IEEE.

[Leon et al., 2017] Leon, L., Kasereka, S., Barin, F., Larsen, C., Weill-Barillet, L., Pascal, X., Chevaliez, S., Pillonel, J., Jauffret-Roustide, M., and Le Strat, Y. (2017). Age-and time-dependent prevalence and incidence of hepatitis c virus infection in drug users in france, 2004–2011: model-based estimation from two national cross-sectional serosurveys. *Epidemiology & Infection*, 145(5):895–907.

[Lofgren, 2017] Lofgren, E. (2017). Systems dynamics models. *Systems Science and Population Health*, pages 77–85.

[Luke and Stamatakis, 2012] Luke, D. A. and Stamatakis, K. A. (2012). Systems science methods in public health: dynamics, networks, and agents. *Annual review of public health*, 33:357–376.

[Maillé and Espinasse, 2005] Maillé, E. and Espinasse, B. (2005). Du couplage de systèmes à l'intégration spatio-temporelle dans les systèmes d'aide à la décision spatiale. *CABM-HEMASMAGET05*.

[McCluskey, 2008] McCluskey, C. C. (2008). Global stability for a class of mass action systems allowing for latency in tuberculosis. *Journal of Mathematical Analysis and Applications*, 338(1):518–535.

[Murphy et al., 2002] Murphy, B. M., Singer, B. H., Anderson, S., and Kirschner, D. (2002). Comparing epidemic tuberculosis in demographically distinct heterogeneous populations. *Mathematical biosciences*, 180(1-2):161–185.

[Ndondo et al., 2016] Ndondo, A., Munganga, J., Mwambakana, J., Saad-Roy, C., Van den Driessche, P., and Walo, R. (2016). Analysis of a model of gambiense sleeping sickness in humans and cattle. *Journal of biological dynamics*, 10(1):347–365.

[Ndondo Mboma, 2017] Ndondo Mboma, A. (2017). *Une Analyse Globale d'un Modèle Mathématique de la Trypanosomiase humaine africaine*. PhD thesis, CRFMI, University of Kinshasa.

[Nianogo and Arah, 2015] Nianogo, R. A. and Arah, O. A. (2015). Agent-based modeling of noncommunicable diseases: a systematic review. *American journal of public health*, 105(3):e20–e31.

[Nkhoma et al., 2012] Nkhoma, W. A., Kibuga, D., Salomao, A., Keita, B., Ndongosieme, A., Wembanyama, H., Roungou, J., and Nkhoma, W. A. (2012). Multidrug-resistant and extensively drug-resistant tuberculosis in the african region. *African health monitor*, 24:25.

[Okuonghae and Ikhimwin, 2016] Okuonghae, D. and Ikhimwin, B. O. (2016). Dynamics of a mathematical model for tuberculosis with variability in susceptibility and disease progressions due to difference in awareness level. *Frontiers in microbiology*, 6:1530.

[Organization, 2018] Organization, W. H. (2018). *WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update*. World Health Organization.

[Organization et al., 2015] Organization, W. H. et al. (2015). Guidelines for surveillance of drug resistance in tuberculosis. Technical report, Geneva: World Health Organization.

[Organization et al., 2016] Organization, W. H. et al. (2016). Global tuberculosis report 2016.

[Organization et al., 2018a] Organization, W. H. et al. (2018a). Global tuberculosis report 2018.

[Organization et al., 2018b] Organization, W. H. et al. (2018b). Latent tuberculosis infection: updated and consolidated guidelines for programmatic management.

[Organization et al., 2018c] Organization, W. H. et al. (2018c). Tuberculosis, (2018).

[Ozcaglar et al., 2012] Ozcaglar, C., Shabbeer, A., Vandenberg, S. L., Yener, B., and Bennett, K. P. (2012). Epidemiological models of mycobacterium tuberculosis complex infections. *Mathematical Biosciences*, 236(2):77–96.

[Passion-Santé, 2015] Passion-Santé (2015). Tuberculose : les symptomes, les risques et les traitements. Accessed: 2018-12-03.

[Pavé, 1994] Pavé, A. (1994). *Modélisation en biologie et en écologie*. Aléas.

[PNLT, 1999] PNLT (1999). Enquête de prévalence sur la résistance tuberculeuse dans la ville de kinshasa.

[PNLT, 2016] PNLT (2016). Guide de technique de prise en charge de la tuberculose intégré aux soins de santé primaire.

[Prats et al., 2016] Prats, C., Montañola-Sales, C., Gilabert-Navarro, J. F., Valls, J., Casanovas-Garcia, J., Vilaplana, C., Cardona, P.-J., and López, D. (2016). Individual-based modeling of tuberculosis in a user-friendly interface: Understanding the epidemiological role of population heterogeneity in a city. *Frontiers in microbiology*, 6:1564.

[Quesnel, 2006] Quesnel, G. (2006). Approche formelle et opérationnelle de la multi-modélisation et de la simulation des systèmes complexes. *PHD trésis Laboratoire d'Informatique du Littoral (LIL). Calais-France*.

[RDC, 2006] RDC, M. S. (2006). Plan stratégique 2006-2011 programme national de lutte contre la tuberculose.

[Rey-Coyrehourcq, 2015] Rey-Coyrehourcq, S. (2015). *Une plateforme intégrée pour la construction et l'évaluation de modèles de simulation en géographie*. PhD thesis, Paris 1-Panthéon-Sorbonne.

[RGC, 2015] RGC (2015). Le shapefile contenant les limites des anciennes provinces de la rdc (11). `https://www.rgc.cd/images/RGCdata/province26.zip`. Accessed: 2018-05-14.

[Rodrigues et al., 2007] Rodrigues, P., Gomes, M. G. M., and Rebelo, C. (2007). Drug resistance in tuberculosis—a reinfection model. *Theoretical population biology*, 71(2):196–212.

[Ronoh et al., 2016] Ronoh, M., Jaroudi, R., Fotso, P., Kamdoum, V., Matendechere, N., Wairimu, J., Auma, R., and Lugoye, J. (2016). A mathematical model of tuberculosis with drug resistance effects. *Applied Mathematics*, 7(12):1303–1316.

[Roux, 2015] Roux, A. V. D. (2015). Health in cities: is a systems approach needed? *Cadernos de saude publica*, 31:9–13.

[Serge Bisuta, 2018] Serge Bisuta, Patrick Kayembe, M.-J. K. H. S. J. D. A. B. G. L. G. M. J.-M. K. (2018). Trends of pulmonary tuberculosis bacteriologically confirmed, treatment outcomes in democratic republic of congo: 2007-2017. *Annales Africaine de médecine, vol 4*, pages 1–20.

[Shannon, 1977] Shannon, R. E. (1977). Simulation modeling and methodology. *ACM SIGSIM Simulation Digest*, 8(3):33–38.

[Sharma et al., 2017] Sharma, A., Hill, A., Kurbatova, E., van der Walt, M., Kvasnovsky, C., Tupasi, T. E., Caoili, J. C., Gler, M. T., Volchenkov, G. V., Kazennyy, B. Y., et al. (2017). Estimating the future burden of multidrug-resistant and extensively drug-resistant tuberculosis in india, the philippines, russia, and south africa: a mathematical modelling study. *The Lancet Infectious Diseases*, 17(7):707–715.

[Siebert, 2011] Siebert, J. (2011). *Approche multi-agent pour la multi-modélisation et le couplage de simulations: application à l'étude des influences entre le fonctionnement des réseaux ambiants et le comportement de leurs utilisateurs*. PhD thesis, Université Henri Poincaré-Nancy 1.

[Simplixi, 2013] Simplixi (2013). Quelle différence entre complexe et compliqué ? `http://www.simplixi.fr/difference-complexe-et-complique/`. Accessed: 2018-04-12.

[Tolk and Muguira, 2003] Tolk, A. and Muguira, J. A. (2003). The levels of conceptual interoperability model. In *Proceedings of the 2003 fall simulation interoperability workshop*, volume 7, pages 1–11. Citeseer.

[Tracy et al., 2018] Tracy, M., Cerdá, M., and Keyes, K. M. (2018). Agent-based modeling in public health: current applications and future directions. *Annual review of public health*, 39:77–94.

[Trauer et al., 2016] Trauer, J. M., Achar, J., Parpieva, N., Khamraev, A., Denholm, J. T., Falzon, D., Jaramillo, E., Mesic, A., du Cros, P., and McBryde, E. S. (2016). Modelling the effect of short-course multidrug-resistant tuberculosis treatment in karakalpakstan, uzbekistan. *BMC medicine*, 14(1):187.

[Trauer et al., 2014] Trauer, J. M., Denholm, J. T., and McBryde, E. S. (2014). Construction of a mathematical model for tuberculosis transmission in highly endemic regions of the asia-pacific. *Journal of theoretical biology*, 358:74–84.

[Trébucq and Schwoebel, 2016] Trébucq, A. and Schwoebel, V. (2016). Numbers of tuberculosis cases: dreams and reality. *The International Journal of Tuberculosis and Lung Disease*, 20(10):1288–1292.

[Tuite et al., 2017] Tuite, A. R., Gallant, V., Randell, E., Bourgeois, A.-C., and Greer, A. L. (2017). Stochastic agent-based modeling of tuberculosis in canadian indigenous communities. *BMC public health*, 17(1):73.

[Van den Driessche and Watmough, 2002] Van den Driessche, P. and Watmough, J. (2002). Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical biosciences*, 180(1-2):29–48.

[Villa, 2001] Villa, F. (2001). Integrating modelling architecture: a declarative framework for multi-paradigm, multi-scale ecological modelling. *Ecological modelling*, 137(1):23–42.

[Vinh et al., 2018] Vinh, D. N., Ha, D. T. M., Hanh, N. T., Thwaites, G., Boni, M. F., Clapham, H. E., and Thuong, N. T. T. (2018). Modeling tuberculosis dynamics with the presence of hyper-susceptible individuals for ho chi minh city from 1996 to 2015. *BMC infectious diseases*, 18(1):494.

[Waldvogel et al., 2012] Waldvogel, F. A., Balavoine, J.-F., Perone, N., and Schusselé-Fillietaz, S. (2012). Les malades complexes: de la théorie des systèmes complexes à une prise en charge holistique et intégrée. *Rev Med Suisse*, 8:1022–4.

[WHO, 2017] WHO (2017). Guidelines for the treatment of drug-susceptible tuberculosis and patient care.

[Wooldridge, 2009] Wooldridge, M. (2009). *An introduction to multiagent systems*. John Wiley & Sons.

[Wooldridge and Jennings, 1994] Wooldridge, M. and Jennings, N. R. (1994). Agent theories, architectures, and languages: a survey. In *International Workshop on Agent Theories, Architectures, and Languages*, pages 1–39. Springer.

[Zeigler and Ören, 1986] Zeigler, B. P. and Ören, T. I. (1986). Multifaceted, multiparadigm modeling perspectives: tools for the 90's. In *Proceedings of the 18th conference on Winter simulation*, pages 708–712. ACM.

[Zhao et al., 2017] Zhao, Y., Li, M., and Yuan, S. (2017). Analysis of transmission and control of tuberculosis in mainland china, 2005–2016, based on the age-structure mathematical model. *International journal of environmental research and public health*, 14(10):1192.

[Zignol et al., 2016] Zignol, M., Dean, A. S., Falzon, D., van Gemert, W., Wright, A., van Deun, A., Portaels, F., Laszlo, A., Espinal, M. A., Pablos-Méndez, A., et al. (2016). Twenty years of global surveillance of antituberculosis-drug resistance. *New England Journal of Medicine*, 375(11):1081–1089.

[Zunga et al., 1998] Zunga, Q., Vagnini, A., Le Page, C., Touré, I., Lieurain, E., and Bousquet, F. (1998). Coupler systèmes d'information géographique et systèmes multi-agents pour modéliser les dynamiques de transformation des paysages. *Modèles et systèmes multi-agents pour la gestion de l'environnement et des territoires*, 25:193–206.